

**Causal Inference Methods for Measurement Error and
Mediation**

by

Yenny G. Webb Vargas

A dissertation submitted to The Johns Hopkins University in conformity with the
requirements for the degree of Doctor of Philosophy.

Baltimore, Maryland

June, 2015

© Yenny G. Webb Vargas 2015

All rights reserved

Abstract

Causal inference provides a principled way to investigate causal effects in public health, neuroscience and other areas. This thesis addresses two topics in causal inference: (i) the estimation of causal effects using covariates measured with error, and (ii) the investigation of mechanisms underlying causal effects. Although covariate measurement error is often present, methods for handling covariate measurement error in propensity score methods have not been widely investigated. We develop an imputation-based solution to using mismeasured covariates in propensity score methods that provide an estimate of a causal treatment effect, and use it to estimate the effects of living in a disadvantaged neighborhood on adolescent mental health and substance use. Furthermore, we can use mediation analysis to study how the causal effect that a treatment X has on an outcome variable Y is influenced by some intermediate variable M . Standard approaches toward assessing mediation require that each of the variables X , M , and Y take scalar values. However, in many situations this may not be reasonable or practical. We extend the standard and causal mediation framework, allowing one or more of the variables to be considered continuous func-

ABSTRACT

tions of time. But making causal statements about mediation always poses a problem because, even if we can randomize the intervention, it is often difficult - or impossible - to randomize the assignment of the mediator. Within-subject designs, common in neuroscience experiments using functional Magnetic Resonance Imaging, open new possibilities for identification of the mediation counterfactuals. We establish a new set of identifiability conditions for estimating causal mediation effects and develop an estimation procedure that is robust to baseline confounding of the mediator-outcome relation. This thesis advances the causal inference literature in innovative ways, enriching the principled thinking about effects and mediation with contributions from the measurement error and functional data analysis literature.

Primary Readers: Elizabeth A. Stuart, Martin Lindquist, Ana Navas-Acien,
and Michelle Carlson.

Secondary Readers: Elizabeth Ogburn, and Peng Huang.

Acknowledgments

I would like to thank:

- first my advisors, Elizabeth Stuart and Martin Lindquist. I have been doubly fortunate, as I have been able to see up close two giants at work. Not only that, they have been amazingly kind and generous with their time, ideas, support, pep talks and insight. I can't believe how lucky I am.
- My loving and cheering husband, who decided to take a chance with me.
- My family and friends. In Monterrey, Singapore, Kansas City, Matamoros, Saltillo, Zacatecas, Topeka, Mexico City, Paris, London, Madrid, Melbourne, Boston, DC, San Francisco, and Baltimore. My mom and dad, who have given me everything they have, and encouraged me to aim high and push through. My mom and dad in law, who always cheered and supported me, and raised the most wonderful man on earth. My siblings, whose love never ceases. To my nieces and nephews, who have made me tía Gaby/Yenny and warm my heart. Melina, who taught me how to meow.

ACKNOWLEDGMENTS

- My doctors, Geshe Kelsang Gyatso, and the Baltimore Sangha, who have shown me a way to be happy and healthy.
- My thesis committee, who have taken the time to review my work, and who have seen me grow as a researcher.
- Lauren Atlas and Tor Wager, for sharing their data and their work in understanding pain.
- The Department of Biostatistics. Karen, Dan and Brian, who believed in me and gave me a chance to shine. To the staff, who keep everything running and gave me their friendship. To the faculty, who provided an amazing training on what it is to do biostatistics. To my fellow students, my dear friends, who shine in a million ways and provide encouragement and examples of success.
- The National Institute of Biomedical Imaging and Bioengineering (5R01EB016061-02; PI: Lindquist.) and the National Institute of Mental Health (R01MH099010; PI: Stuart.) who supported my work.
- Ruth Pfeiffer and the Biostatistics Branch of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, for giving me an opportunity to learn from the best, and for supporting my studies.

Dedication

A mi esposo, mi compañero de aventuras, de batallas, y de victorias. Mi roca, mi base, y mi centro. Verdaderamente no habría logrado esto sin ti.

A toda mi familia y todos mis amigos.

A todas las personas que sufren de altibajos.

Que este trabajo contribuya a incrementar la felicidad y el bienestar de todos.



To my husband, my partner in adventure, battle and victory. My rock, my home, and my heart. I truly would not have done this without you.

To all my family and all my friends.

To all people who suffer from ups and downs.

May this work contribute to increase the happiness and welfare of all.

Contents

Abstract	ii
Acknowledgments	iv
List of Tables	xi
List of Figures	xii
1 Introduction	1
1.1 Causal Inference	5
1.2 Causal Mediation	10
1.2.1 Causal mediation effects	17
1.2.1.1 Natural effects	17
1.2.1.2 Controlled effects	20
1.2.1.3 Principal strata effects	21
1.3 Measurement Error	24
1.3.1 Types of measurement error	25

CONTENTS

1.3.2	Methods for correction	26
1.4	Functional Data Analysis	26
1.4.1	Functional data models	30
1.4.1.1	Function-on-scalar regression	30
1.4.1.2	Scalar-on-function regression	31
1.4.1.3	Function-on-function regression	31
1.4.1.4	Estimation	32
1.5	Overview of the dissertation	32
2	Propensity Score Analysis with Covariate Measurement Error	34
2.1	Propensity scores and the importance of accurate covariate measurement	37
2.1.1	Inverse Probability of Treatment Weighting	39
2.2	Measurement error and propensity score methods	41
2.2.1	The naive method	43
2.2.2	Multiple imputation for external calibration	43
2.3	Simulation Study	46
2.3.1	Methods compared	46
2.3.2	Data Generation - Normally distributed simulation	47
2.3.3	Data Generation - Non-normally distributed simulation	50
2.3.4	Results	51
2.3.4.1	Normally-distributed simulation	51
2.3.4.2	Non-normally-distributed simulation	54

CONTENTS

2.4	Illustrative Example	55
2.4.1	Overview and set-up	55
2.4.2	NCS-A Results	58
2.5	Discussion and Conclusion	60
3	Functional Mediation Analysis	64
3.1	Introduction	64
3.2	Mediation Analysis	69
3.3	Functional Mediation Analysis	71
3.4	Estimation	75
3.5	Inference	77
3.5.1	Causal interpretations	79
3.6	Simulation Study	80
3.7	Data example 1: What part of a continuous pain rating matters most to pain recall?	87
3.8	Data example 2: How do different brain regions communicate in re- sponse to pain?	91
3.9	Discussion	96
4	Within-Subject Designs for Causal Mediation Analysis	98
4.1	Introduction	98
4.2	Thermal Pain Experiment	100

CONTENTS

4.3	Within-subject causal mediation	102
4.3.1	Identification of sub-trials	103
4.3.2	Identification of causal mediation effects	108
4.3.3	Estimation and inference	113
4.4	Application to Thermal Pain Experiment	115
4.4.1	Within-subject estimation	116
4.4.2	Population-level estimation and inference	118
4.5	Discussion	121
5	Conclusion	124
6	Appendix	129
6.1	Appendix for Chapter 2: Simulation details and code	129
6.2	Appendix for Chapter 3: Assumptions for causal identification of mediated effects	130
6.2.1	Scalar-Scalar-Function model	131
6.2.2	Scalar-Function-Function model	133
6.3	Appendix for Chapter 3: Simulation details and code	136
	Bibliography	137
	Vita	156

List of Tables

2.1	Values of parameters used in simulations for the use of multiple imputation with external calibration in propensity score analysis	49
-----	--	----

List of Figures

1.1	Depiction of mediation	12
1.2	Example of functional data: BOLD contrast measured in two brain regions	29
2.1	Structure of the data in an observational study with external calibration	42
2.2	Results from the normally-distributed simulation comparing the proposed congenial MI-EC method with the truth, the naive approach, and the uncongenial MI-EC	52
2.3	Estimates for the average effect of living in a disadvantaged neighborhood on risk of having a current substance abuse dependence disorder and anxiety or depressive disorder for adolescents living in disadvantaged neighborhoods	59
3.1	Simple path model	65
3.2	Functional mediation models	68
3.3	Estimates for parameters in scalar-function-scalar mediation models simulated under the four scenarios	82
3.4	Estimates in scalar-scalar-function mediation models simulated under the four scenarios	84
3.5	Estimates in scalar-function-function mediation models simulated under the four scenarios	86
3.6	Path model for continuous pain rating	87
3.7	Mediator model estimated functions for continuous pain rating	88
3.8	Outcome model point estimates for continuous pain rating	89
3.9	Estimated β and $\alpha\beta$ function decomposition for continuous pain rating	90
3.10	Estimated direct and indirect effects for continuous pain rating	90
3.11	Path model for brain connectivity	92
3.12	Mediator model estimated path coefficients for brain connectivity	93
3.13	Outcome model estimated path coefficients for brain connectivity	93

LIST OF FIGURES

3.14	Estimated $\beta(s, t)$ and $\alpha(s)\beta(s, t)$ function decomposition for brain connectivity	94
3.15	Estimated direct and indirect effects for brain connectivity	95
4.1	Within-subject estimates of functional coefficients for brain mediation of pain	117
4.2	Across-subject estimates of functional coefficients and causal mediation effects for brain mediation of pain	119

Chapter 1

Introduction

The field of causal inference has provided many advances to statistics and other fields, like epidemiology, economics, and computer science. It provides a principled way to assess in which situations one can infer causality. It has also lead to the development of new methods for estimating effects that maintain desirable properties, such as robustness to incorrect specification of the proposed models. Having a principled way to assess causality has been crucial in the analysis of mediation, while model robustness is a property of propensity score analysis.

The present work addresses some complications that arise in the practice of public health and neuroscience. For example, variables are often assumed to be measured without error, but a degree of error in measurements will often be present. Important variables like socioeconomic status, depression, nutrient intake, or exposure to pollution are difficult to quantify in a precise manner. Moreover, variables that are

CHAPTER 1. INTRODUCTION

functions of time, like the brain blood response to neuronal function, or the cumulative exposure to pollutants, may be complex in nature. Reducing them to simple scalars results in loss of useful information. Finally, advances in causal inference derived from randomized experiments, and the new experimental designs that are used in neuroscience call for new sets of assumptions to address causality.

When the data to be used have already been collected and the treatment of interest¹ was not randomly assigned, or when it is impractical or unethical to randomize the treatment, a strategy for estimating the treatment effect is to construct groups that are comparable in all variables that can affect both the treatment assignment and the outcome. These are called confounding variables, as they confound the relation between treatment and outcome, and can even induce a relation solely on their effect on both treatment assignment and outcome. When creating comparable groups, propensity score methods rely on measuring the confounders correctly. If there is error in the measurement of the confounders, the groups created with propensity score methods may not be comparable in terms of the true underlying confounders. In chapter 2, I describe how using mismeasured covariates in propensity score methods leads to bias in the estimate of the causal treatment effect, and I present a method that can correct for this bias. I then apply this method to estimate the effect that living in a disadvantaged neighborhood has on adolescent drug use.

Meanwhile, learning how a treatment works can help us understand the biological

¹We consider a treatment to be the independent variable, one that we would modify ourselves if it were possible, and whose effect is of interest.

CHAPTER 1. INTRODUCTION

or psychological mechanism behind it, and can lead to its improvement. In order to do this, we can pose whether an intermediate variable lies in the causal pathway between the treatment and an outcome. That is, we pose whether the treatment modifies the intermediate variable, which in turn changes the outcome. If so, we can say that the intermediate variable mediates the effect of the treatment, and call it a ‘mediator’.

There are methods to assess mediation, and while they may allow for multiple mediators, the majority assume that the variables in question are all scalar in value. However, there are variables that have a more complex structure, as they may be functions of time or space. For example, we can have a measure of brain activation by quantifying the changes in blood dynamics that result from neuronal function. These changes appear right after neurons transmit their impulses, and last roughly 30 seconds. We could investigate how the history of activation in one brain region may mediate the response to thermal pain in a second region, but this requires the development of new methods. In chapter 3, I extend the mediation framework to accommodate mediators and outcomes that are functions of time (also known as ‘functional data’ or ‘intensive longitudinal data’), and apply it to estimating functional connectivity, or how different brain regions work together.

It is generally difficult to claim that the mediated effects are actually causal effects. This would imply that the treatment caused the mediator to change, and then the mediator caused the outcome to change. In order to defend this, we need to assume

CHAPTER 1. INTRODUCTION

that the intervention is not affected by variables that also affect the outcome (which in many cases can be true as the treatment may be randomly assigned), but we also need to assume that the mediator is not affected by variables that also affect the outcome other than the treatment (which is not necessarily true as we usually do not randomize the mediator.) In chapter 4, I describe how a particular experimental design can overcome limitations in traditional causal mediation analysis. This design is common in neuroscience experiments, and it involves applying multiple treatments to each participant, often with replicates. Therefore, we can compute a causal effect for each person, and estimate a population effect by averaging the individual causal effects.

In each chapter, I illustrate how the proposed statistical methods can solve a question in public health or neuroscience. I connect the three topics previously discussed in chapter 5, proposing ideas to move the statistical fields forward, and describing other areas of application in public health.

The rest of this chapter is structured as follows. I begin by introducing the field of causal inference in section 1.1, and addressing causal mediation analysis in section 1.2. I then briefly describe the study of measurement error in section 1.3 and refer to functional data analysis in section 1.4.

1.1 Causal Inference

The potential outcomes framework¹⁻³ has provided a principled way to define causal effects. It relies on three components: a set of treatments, units that receive the treatments, and potential outcomes that result from units receiving the treatments at a particular time. It then defines causal effects in terms of the potential outcomes, and establishes a set of assumptions that pair the potential outcomes to observed outcomes. The latter pairing is referred to as the ‘identification of the potential outcomes’.

Our first motivating example is the following. We are interested in estimating the average treatment effect that living in a disadvantaged urban neighborhood has on adolescent drug use for adolescents surveyed in the National Comorbidity Survey Replication Adolescent Supplement (NCS-A) as described in Rudolph *et al.*⁴ In this case, the units are adolescents in the NCS-A survey, and the treatment is ‘being assigned to live in a disadvantaged neighborhood’. Let Z represent the type of neighborhood in which an adolescent lives, with $Z = 1$ for living in a disadvantaged urban neighborhood, and $Z = 0$ for living in a non-disadvantaged urban neighborhood. Then, each adolescent has two potential outcomes at the time of the study - their drug use if they live in a disadvantaged urban neighborhood ($Y(Z = 1)$) and their drug use if they live in a non-disadvantaged urban neighborhood ($Y(Z = 0)$). These potential outcomes are defined for all adolescents, so if adolescent i lives in a disadvantaged urban neighborhood at the time of the study, she has a pattern of

CHAPTER 1. INTRODUCTION

drug use related to that condition $Y_i(Z_i = 1)$, and she also has a pattern of drug use related to the control condition $Y_i(Z_i = 0)$. The latter means that she has a potential outcome in a scenario were she lives in a non-disadvantaged neighborhood at the time of the study as well.

The average treatment effect is defined in terms of the potential outcomes; it could be their difference, their quotient, or other type of comparison. It can also be defined in terms of the population of interest. We can define the average treatment effect among all adolescents living in urban neighborhoods, regardless of whether they are disadvantaged or not, or we can restrict our analysis to a subset of the population. In our case, we are interested in making inferences only for adolescents who do live in disadvantaged urban neighborhoods, by comparing their drug use in the neighborhood they live in against their potential drug use had they lived in a non-disadvantaged neighborhood during the same period. This comparison can be written as: $E[Y_i(1 | Z_i = 1) - Y_i(0 | Z_i = 1)]$. This is called ‘the average treatment effect on the treated’ (ATT), because it is an average only among adolescents receiving the treatment, not the entire population of adolescents.

In order to estimate the ATT, we need to somehow measure the two potential drug uses for adolescents living in a disadvantaged neighborhood: their use had they lived in a disadvantaged neighborhood, and their use had they lived in a non-disadvantaged neighborhood during the same period. The set of assumptions that help us map the potential outcomes on to observable quantities are called ‘identifying assumptions’.

CHAPTER 1. INTRODUCTION

First, we assume that, if we assign adolescent i to living in neighborhood type z , we would get to observe their potential drug use under life in neighborhood type z (the consistency assumption, see Cole and Frangakis⁵). We also assume that the potential drug use of one adolescent in the sample does not influence the potential drug use of another in the sample, and that each type of neighborhood only has one version, known as the Stable Unit Treatment Value Assumption (or SUTVA^{6,7}). Let $\mathbf{Z} = \{Z_1, \dots, Z_n\}$ be the vector of assigned treatments for all adolescents in the study, the SUTVA is represented as:

$$Y_i(\mathbf{Z}) = Y_i(\mathbf{Z}') \quad \text{if} \quad Z_i = Z'_i. \quad (\text{A1})$$

This implies that if we were to have two experiments, in one we have a particular assignment of treatments (\mathbf{Z}) where adolescent i lives in a disadvantaged neighborhood ($Z_i = z_i$), and in the other we permute the assignment (\mathbf{Z}') but still have adolescent i living in a disadvantaged neighborhood ($Z'_i = z_i$), the potential outcomes of adolescent i in both experiments would be the same. That is, if the treatment assignment for adolescent i remains the same, and $Z_i = Z'_i = z_i$ then the potential outcomes are the same, even if the treatment for other adolescents change.

Given assumption (A1), we can write:

$$(Y_i(z) \mid Z_i = z) = (Y_i^{obs} \mid Z_i = z).$$

CHAPTER 1. INTRODUCTION

In other words, when we assign adolescent i to live in a disadvantaged neighborhood, we do observe the potential outcome of that individual living in a disadvantaged neighborhood. Examples when this assumption may not hold are if there are cases where adolescent i lives in a neighborhood that, in different scenarios, has different levels of disadvantage (the treatment varies). Another example of violations of SUTVA is when the fact that adolescent i lives in a disadvantaged neighborhood affects the drug use of another adolescent j in the study (and therefore it changes its potential outcomes, this phenomenon is called ‘interference’).

How do we ever get to see what would happen under living in a non-disadvantaged neighborhood for those adolescents who live in a disadvantaged neighborhood? If the treatment were randomized, people experiencing one type of treatment would look, on average, very similar to the people experiencing the other type of treatment. Therefore, we can take the results of people under treatment z and have those stand for what would have happened to people in treatment z' had they had treatment z . In our case, it would mean that we take the drug abuse levels in the group living in non-disadvantaged neighborhoods and pass them for what would have happened to adolescents in disadvantaged neighborhoods had they not lived in disadvantaged neighborhoods.

But there are many baseline factors that differ between the two groups that render them nonexchangeable, like their distribution of gender, current age, race/ethnicity, region of the country in which they live, family income, family structure, and age of

CHAPTER 1. INTRODUCTION

the mother at which she gave birth to the adolescent in question (more details on this can be found in Rudolph *et al.*⁴) If we find two adolescents that are equal in all these factors, except that one lives in a non-disadvantaged neighborhood while the other lives in a disadvantaged one, we could exchange their results (if we think that no relevant variable is missing.) The assumption that, within a fixed level of all the relevant factors taken into account, the choice of treatment assignment is as if by the flip of a coin, is called ‘conditional ignorability of treatment assignment’.⁸ We use a stronger version that also assumes that every adolescent has a chance of living in either type of neighborhood, called the ‘positivity’ assumption.

If we were to find a match for every adolescent in the sample, we could create two groups where the distribution of relevant factors was the same and they only differed on the treatment they received. But even if the sample size was large, getting exact matches on a large list of factors may not be possible. This is why getting one variable that, if you match on its value you will create two groups that have the same distribution of relevant covariates, is very useful. This variable is the propensity score, and it can balance the distribution of all covariates that are used to calculate it. The propensity score, first introduced by Rosenbaum and Rubin,⁸ is formally defined as the probability of receiving treatment, given the observed covariates. There are many methods that use the propensity score to ensure a fair comparison of treatment and control groups,⁹ and they often perform better than the commonly used method of regression adjustment.¹⁰ Propensity score methods have become a common tool

for estimating causal effects in non-experimental studies, as suggested by the more than 13,000 citations² of the 1983 seminal paper by Rosenbaum and Rubin.⁸

1.2 Causal Mediation

When we look at the effect that a treatment, intervention, or variable has on an outcome, we often ask questions about the mechanism behind it. For example, if we hold a hot cup of coffee for too long, we may begin to feel pain. We can ask ‘Is a particular brain region responsible for the perception of this thermal pain?’ Opening the black box to investigate the mechanism and find out how a treatment works can lead to better interventions that stem from a deeper understanding of the problem at hand. We need to open the box carefully in order to not mistake association for causation; even if the treatment was randomized, the variables that encompass the mechanism are not necessarily free from confounding with the outcome. Therefore, making causal claims will require assumptions about the presence of confounders of this relation. Nevertheless, we would like to make causal claims about the mediator that can help develop policies, and strengthen our belief in the proposed mechanism.

We usually propose a mechanism involving one or more variables and design an experiment that includes them as well as the treatment and the outcome. We refer to the variables in the proposed mechanism as ‘mediating variables’ or ‘mediators’. In our example, the activation of a particular brain region of interest will be the mediator,

²As measured by Google Scholar on May 2015.

CHAPTER 1. INTRODUCTION

while holding the cup of coffee for too long is the treatment, and our experience of pain is the outcome. In many cases, the proposed mechanism may exclude other variables that are at play. Figure 1.1 represents three possible cases that may apply to our proposed mechanism. The first (1.1a) depicts the case where the mechanism proposed accounts for all the effect that the treatment has on the outcome. In our first example, if we could follow the activation in the whole brain (instead of region by region), we could assume that we have the complete mechanism. If we only focus on the activation of one brain region, we would find that the rest of the brain regions are also being modified by the treatment. In this case, we would observe an effect that is not accounted for by our proposed mechanism, as depicted in figure (1.1b). Or it could be that there is a variable that is associated with the mechanism and the outcome, and we could potentially observe a relation between the mediator and the outcome because both vary according to such variable. It could be that there is an underlying ‘pain resilience’ characteristic that certain individuals have, and this trait affects their brain activation, as well as their pain rating. This reflects a confounded mediator-outcome relation and is illustrated in figure (1.1c).

In figure (1.1b), we can partition the total effect that the treatment or intervention has on the outcome into an effect that arises from the changes that the treatment has on the mediator, and the subsequent changes that the mediator produces on the outcome (termed ‘indirect effect’); and the effect that the treatment has on the outcome regardless of the changes it produced on the mediator (termed ‘direct effect’).

CHAPTER 1. INTRODUCTION

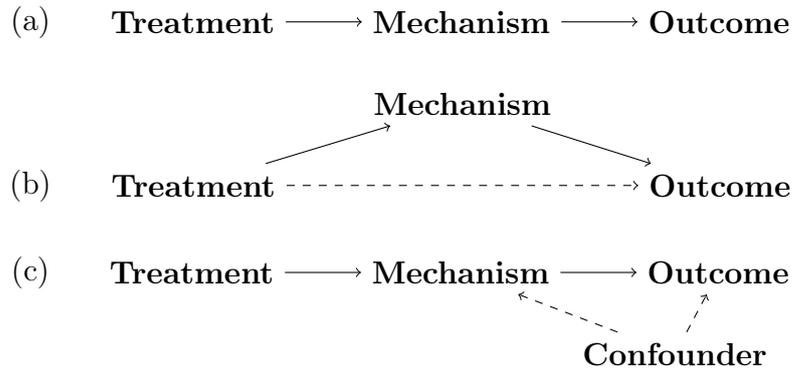


Figure 1.1: Depiction of mediation: (a) Complete mechanism. (b) Incomplete mechanism. (c) Confounded mechanism. The solid lines represent the effects that are related to the mechanism, while the dashed lines represent effects that are not.

We are interested in making inferences about the indirect effect.

Several methods have been proposed to assess indirect effects. Judd and Kenny¹¹ and Baron and Kenny¹² introduced a popular approach to estimate direct and indirect effects (the number of citations registered in Google Scholar is 50,435 for the second, and 1,604 for the first). Their method popularized path analysis and regression models within the social sciences and is related to structural equations models. Vanderweele¹³ presents a clear comparison of approaches to assess mediation, including the Baron and Kenny regression technique, structural equation modeling, causal graphs, and marginal structural models. To illustrate the regression approach, as well as the causal mediation approach, consider a trial to examine how the brain processes thermal pain,¹⁴ participants received randomly either a high heat (noxious) stimulus³ to their forearm, or a low heat (non-noxious) stimulus. Researchers were interested

³The high heat stimulus was the equivalent to ‘holding a hot cup of coffee for too long. It is painful, but does not burn’.

CHAPTER 1. INTRODUCTION

in assessing how the change in temperature led to changes in brain activation and a particular pain experience. Let Z_i be the random variable of treatment assigned to individual i , with $Z_i = 1$ if the stimulus used high heat, and $Z_i = 0$ when it used low heat. Let M_i be the level of brain activation in our brain region of interest, and let Y_i be the reported experienced pain.

The traditional method relies on three linear models:

$$\begin{aligned}M_i &= d_1 + aZ_i + e_{1i} \\Y_i &= d_2 + cZ_i + e_{2i} \\Y_i &= d_3 + bM_i + c'Z_i + e_{3i}.\end{aligned}\tag{1.1}$$

The first analyzes the association of a heat stimulus (Z_i) with levels of brain activity (M_i). The second analyzes the association of the heat stimulus (Z_i) with reported pain (Y_i). This would be the ‘total effect’ of the heat stimulus on pain report. Finally, the third analyzes the association of heat stimulus (Z_i) and a particular level of brain activation (M_i) with reported pain. The ‘mediated effect’ (indirect effect) is the product $a \times b$, which in this setting is also equivalent to $c - c'$. Sobel¹⁵ presents asymptotic standard error errors for $\hat{a} \times \hat{b}$, while MacKinnon et al.¹⁶ present the McGuigan and Langholz variance estimator for $\hat{c} - \hat{c}'$.

The method by Judd and Kenny¹¹ assumes that the errors e_{1i} , e_{2i} , e_{3i} , are normally

CHAPTER 1. INTRODUCTION

distributed and independent across individuals, that e_{1i} and e_{3i} are independent for each individual, and that there is no interaction between the effects of the treatment and mediator on the outcome. The assumption of independence of the errors e_{1i} and e_{3i} is equivalent to assuming there are no confounders of the mediator-outcome relation.

We illustrated the simple case that is defined by three linear models, in which the correlations among variables are of interest. More complex mechanisms can be accommodated by incorporating more linear regressions as well as assumptions about the correlation of the error terms, which is equivalent to modeling the covariance structure. This represents the structural equation modeling framework or path analysis.^{17, 18}

The traditional framework makes inferences concerning parameters that involve the observed values, and that cannot be interpreted as causal without making assumptions, see Jo¹⁹ for a clear description of these. On the other hand, the structural equation framework approaches causality by defining a causal hypothesis that leads to a particular covariance structure, which is tested against the observed covariance structure. They do assume that there are no unmeasured confounders among the proposed structure.¹⁸

We approach causality with the use of the potential outcomes framework. Let $M_i(z)$ represent the potential mediator⁴ when the treatment in $Z = z$, and $Y_i(z, M_i(z))$

⁴Since we use ‘outcome’ only to refer to Y_i , we refrain from calling the possible responses of the mediator ‘potential outcomes of the mediator’. We refer to them as ‘potential mediators’.

CHAPTER 1. INTRODUCTION

represent the potential outcome associated to having treatment $Z = z$ and the potential mediator $M_i(z)$.

We define the ‘total effect’ of the treatment on the outcome as:

$$E(Y_i(1) - Y_i(0)) = E(Y_i(1, M_i(1)) - Y_i(0, M_i(0))); \quad (1.2)$$

this is the average causal effect of the treatment on the outcome, as introduced before. This would be the effect of assigning a participant i to receive a high heat stimulus, as compared to receiving a low heat stimulus, on their pain report.

So far, the potential outcomes that we had considered have been $Y_i(1, M_i(1))$ and $Y_i(0, M_i(0))$. When considering the effect of all the levels of potential mediators on the potential outcomes, we will consider a large number of the latter. For example, we can think of having four potential outcomes:

$$Y_i(1, M_i(1)), \quad Y_i(0, M_i(0)) \quad (1.3)$$

$$Y_i(1, M_i(0)), \quad Y_i(0, M_i(1)). \quad (1.4)$$

In this case we only imagine potential mediator levels induced by the treatment. The potential outcomes only require thinking about the brain response that happens when a participant has a high heat stimulus ($M_i(1)$), or that which happens when he has a low heat stimulus ($M_i(0)$).

If we consider all the potential outcomes for all the possible values that the me-

CHAPTER 1. INTRODUCTION

diator can have, we would be thinking about all the possible pain reports that a participant could have resulting from having no brain activation to the maximum brain activation possible. We are thinking about an infinite number of potential outcomes of the form:

$$Y_i(1, m), \quad Y_i(0, m) \quad \forall m \in [0, \infty). \quad (1.5)$$

In the first case, we have imagined that the potential outcome $Y_i(1, M_i(0))$ exists, that the situation in which we assign participant i to receive a high heat stimulus, but somehow such participant actually has the mediator levels that she would have had she received a low heat stimulus ($M_i(0)$), is a possible future at the beginning of the trial. We also imagined the contrary case of having participant i receive a low heat stimulus, but have mediator levels associated with a high heat stimulus. In equation (1.5), we further imagine that it is possible that a participant i received a high heat stimulus, and also has any possible level of brain activation.

We should consider whether these assumptions are likely to hold in our scientific problem, or not. In the case of the pain trial, a technique called transcranial magnetic stimulation²⁰ allows for the temporary activation or deactivation of brain regions via a safe, non painful, and noninvasive procedure, and we could manipulate the mediator in this sense. Pearl²¹ and Egleston²² argue in further detail about the relevance of

CHAPTER 1. INTRODUCTION

these assumptions. The first poses how one set of potential outcomes may be more relevant when the relation between the mediator and the treatment is of interest, against settings where the policy objectives are of interest; while the second consider cases in which it is not possible to imagine experiments with which the potential outcomes in equation (1.4) can be observed.

1.2.1 Causal mediation effects

Given that there are a variety of potential outcomes related to changes in the potential mediators, there are many ways in which we can define comparisons among them. We will describe three types of comparisons, and we refer to them jointly as causal mediation effects. For the first two causal mediation effects, following Robins and Greenland²³ and Pearl,²¹ we refer to them as natural effects and controlled effects. We will also consider principal strata effects, whose use in mediation inference has been described as well.^{19,24–26}

1.2.1.1 Natural effects

Natural effects^{521,23} make inferences that only require considering potential outcomes and potential mediators that arise from changing the treatment status (as in equations 1.3 and 1.4). They are also considered ‘descriptive’ effects, and are useful when the values of the mediator are conceptually tied to the treatment. In such cases,

⁵Pearl²¹ calls them natural effects, while Robins and Greenland²³ call them pure effects

CHAPTER 1. INTRODUCTION

we cannot imagine having mediator levels different from the ones achieved through the different treatments.

The natural direct effects are the average causal effect of Z_i on Y_i that is caused beyond changes in the mediator:

$$E(Y_i(1, M_i(z)) - Y_i(0, M_i(z))). \quad (1.6)$$

In the pain trial, this amounts to comparing two futures where both have achieved the same level of brain activation ($M_i(z)$), but one of them was under high heat while the other was under low heat.

The natural indirect effects are the average causal effect of Z_i on Y_i that is only due to the change in the mediator:

$$E(Y_i(z, M_i(1)) - Y_i(z, M_i(0))). \quad (1.7)$$

In this case, we hold constant the intervention at $Z_i = z$ and only vary the mediator for ‘natural’ levels, those associated with each treatment. This would be the difference between the potential outcomes where in both cases we assign participant i to receive a high heat stimulus, and we only change the levels of brain activity from those that the participant would have if they had a high heat stimulus to those that arise when they receive a low heat stimulus.

CHAPTER 1. INTRODUCTION

Given this set up, we have two natural direct effects: one arises when we fix the mediator at the level corresponding to the control group, another when we fix the mediator to the level of the treatment group. We also have two natural indirect effects depending on which value of the treatment we choose to hold.

The total effect in (1.2) can be decomposed into the natural direct and indirect effects. Adding and subtracting $Y_i(1, M_i(0))$ to equation (1.2) produces

$$\begin{aligned} E(Y_i(1, M_i(1)) - Y_i(0, M_i(0))) &= E(Y_i(1, M_i(1)) - Y_i(1, M_i(0)))^* + \\ &E(Y_i(1, M_i(0)) - Y_i(0, M_i(0)))^{**}, \end{aligned}$$

where the 'total' effect of treatment Z_i has been decomposed into an effect solely due to the change in the mediator level given by the treatment (*, one of the natural indirect effects), and an effect of the treatment that is not due to a change in the mediator (**, one of the natural direct effects). The decomposition is not unique, as another can be obtained when adding and subtracting $Y_i(0, M_i(1))$.

One of the advantages about the natural effects is that they do not require a particular structure or model imposed on the form of the potential outcomes, nor on the potential mediators, nor on the expectation of either. Another advantage is that, for the use of natural effects, we need to consider only four potential outcomes, and only think about two that cannot arise naturally within the defined experiment

CHAPTER 1. INTRODUCTION

(the potential outcomes $Y_i(1, M_i(0))$ and $Y_i(0, M_i(1))$). We still need to think that it is possible to have an external intervention in which we, for each participant, can change artificially the levels of brain activity from those that arise from having a high (or low) heat stimulus, to those of the contrary intervention.

1.2.1.2 Controlled effects

Controlled effects²¹ make inferences that envision potential outcomes that correspond to having mediator levels set at a particular value, not necessarily achieved through the intervention. They are also considered as ‘prescribed’ effects, and are of interest when it is possible and desirable to control the mediating variable by itself.

The controlled direct effect is defined as the effect that the treatment has given that we fix the mediating value at m :

$$E(Y_i(1, M_i = m) - Y_i(0, M_i = m)), \quad (1.8)$$

which amounts to the effect of giving a high heat stimulus to a participant while keeping the level of brain activation at m .

We would also like to estimate the controlled effect of the mediator;^{27,28} that is, the effect of having a set change $(m - m')$ in the mediator while we fix the treatment at z :

$$E(Y_i(z, M_i = m) - Y_i(z, M_i = m')), \quad (1.9)$$

when $z = 1$, it is the effect of artificially changing the level of brain activity from m to m' in a participant that receive a high heat stimulus.

Kaufman et al.²⁹ and VanderWeele³⁰ remark that the total effect cannot be decomposed into the sum of a controlled direct and indirect effect, unless one assumes that there is the relation between the outcome and the mediator does not vary among levels of the treatment (there is no interaction between the treatment and the mediator effect on the outcome).

To consider the controlled effects, we need to be able to consider a potential outcome in which we can intervene on the treatment and also on the mediator. In our example, we need to consider that it is possible to give a participant a high heat stimulus and, at the same time, artificially increase or decrease the level of brain activity to a level m . We could think that we could stimulate the brain directly to attain the level m .

1.2.1.3 Principal strata effects

The principal stratification framework³¹ has also been used to define and estimate causal mediation effects.^{19,25,26} This framework only considers potential outcomes

CHAPTER 1. INTRODUCTION

that can occur and are consistent with what is observed in the data. In contrast, natural and controlled effects require potential outcomes of the form $Y_i(1, M_i(0))$, which cannot be observed in practice except in certain experimental designs.³² Moreover, this framework uses the complete set of potential mediators to define strata, making the strata independent of the treatment assignment.

For this example, we will categorize the mediator (levels of brain activity) into two groups, those that showed a decrease or maintenance in brain activity levels when compared to baseline, and those that showed an increase with respect to baseline levels. Given a binary mediator, we can define four underlying principal strata:

- 1. Forward-responders** Those who would have the mediator value 1 when assigned to treatment, and have mediator level 0 when assigned to control. In our example, this could be defined as the group where the high heat stimulus would highly increase the levels of brain activity, while the low heat stimulus would have no effect on brain activity.
- 2. Backward-responders** Those who would have the mediator value 0 when assigned to treatment, and have mediator level 1 when assigned to control. This group is the opposite of group 1, and is composed of participants that show no change in the level of brain activity when they receive a high heat stimulus, but show an increase of it under a low heat stimulus.
- 3. Always-responders** Those who would have the mediator value 1 when assigned

CHAPTER 1. INTRODUCTION

to treatment, and have mediator level 1 when assigned to control. In the pain trial, the group is composed of participants that would have an increase in brain activity under a high or low heat stimulus.

4. Never-responders Those who would have the mediator value 0 when assigned to treatment, and have mediator level 0 when assigned to control. These participants would have no change in brain activity, whether receiving a high or a low heat stimulus.

Let $S_i \in \{1, 2, 3, 4\}$ represent the principal strata that corresponds to individual i . The average causal effects are defined in terms of the strata j :

$$E(Y_i(1) - Y_i(0) \mid S_i = j), \tag{1.10}$$

within each strata, we compare the effect of receiving a high heat stimulus to receiving a low heat stimulus. Jo¹⁹ compares the traditional framework to the principal stratification framework, and finds the assumptions that render the parameters from each framework to have the same interpretation. Although these principal strata effects have comparable characteristics as the direct and indirect effects, they cannot be directly interpreted as such, since we do not fix the mediator levels for every individual. Even if we could fix the mediator levels, Jo et al.²⁶ describe how the interpretation of the principal strata effects does not correspond to the usual direct and indirect

effects.

The framework can be extended to continuous mediators (intermediate variables), as in Jin and Rubin,^{33,34} but it requires stronger assumptions.¹⁹

1.3 Measurement Error

Many variables cannot be measured perfectly. If we look at the effect of diet cholesterol on weight, would we measure the exact amount that a person ingests in a day? Over a year? How about the weight of the person? A person's weight has biological variation due to physiological processes, and technical variation due to the instruments used used to measure. Moreover, we can be interested in variables that are latent constructs that cannot be directly observed. However, making inferences about the effect of mismeasured variables has been shown to be biased when measurement error is not addressed.^{35,36}

Estimating parameters when variables are measured with error require three ingredients. The first is the model for the parameters, defined in terms of the true variables. The second is the measurement error model, which defines how the mismeasured variables relate to the true variables. The third is additional information about the measurement error, which can be: knowledge of the parameters in the measurement error model, having replicates of the mismeasured variable, having a validation or calibration data set with information on both true and measured vari-

ables, having instrumental variables.

Even though the prevalence of measurement error is high, the implications of using mismeasured covariates is not well studied in causal inference. More research is needed to address this, as well as provide methods for its correction.

1.3.1 Types of measurement error

From the point of view of variance structure, measurement error can be divided into two types. In classical measurement error, the measured variable arises from a true variable measured with added noise, so we can make assumptions about the distribution of the measured values given the true values. In contrast, Berkson measurement error posits that the true variable has more variability than the measured variable, and we can make assumptions about the distribution of the true variable conditioning on the measured variable.

Classical measurement error. In the simplest form, the classical measurement error model is:

$$W = X + e$$

where e has a particular distribution centered at zero with some variance σ_e^2 . This model has additive error and unbiased expectation. Given this model, we can define reliability as

$$r = \sigma_X^2 / \sigma_e^2.$$

CHAPTER 1. INTRODUCTION

An adolescent's recall of the age at which her mother gave birth to her, or the added noise that the magnetic resonance machine adds to the measure of BOLD contrast are examples of this type of error.

Berkson error The Berkson error can be written as $X = W + e$, the true exposure X has more variability than the one measured by the proxy W . This type of error is common in environmental studies, where a particular pollutant is measured at stations, and the true exposure varies from person to person.

1.3.2 Methods for correction

Using mismeasured variables in linear and non-linear models leads to bias in estimated parameters. To correct for such bias there are direct-bias corrections, moment-based methods, use of instrumental variables, regression calibration, simulation-extrapolation (SIMEX), and modifying estimating equations.^{35–37}

1.4 Functional Data Analysis

Data that in principle come from a continuous process in time or space are called 'functional data'. For example, physiological measures do not change abruptly. Our height changed smoothly over time as we grew from birth to the present day. It was defined for all times between birth and today. Therefore, we can think that our height was defined for an infinite number of time points.

CHAPTER 1. INTRODUCTION

There are methods that have been developed to make inferences about functional data. But first, we will go into detail about the data collected in the motivating example introduced in Section 1.2.

In the pain study,¹⁴ there are twenty participants that receive either a heat stimulus (Z_i) while inside the fMRI scanner. The stimulus can be low heat ($Z_i = 0$), or high heat ($Z_i = 1$). Brain activation is considered to be the chemo-electrical response at the neuron level.³⁸ Unfortunately, measuring neuron activation at the same time and throughout the whole brain is not yet feasible (it is only feasible for areas close to the surface of the brain using electroencephalograms), therefore other methods have been developed to approximate this. One such method is functional magnetic resonance imaging (fMRI), which takes advantage of other processes that accompany the electric potentials. The signal transmission requires an uptake of oxygen and glucose from the blood supply, which increases blood flow to the activated tissue (termed ‘hemodynamic response’). With the uptake of oxygen, hemoglobin becomes deoxyhemoglobin, which has magnetic properties that can be traced with fMRI.³⁹

The fMRI time series captures the hemodynamic response across time within small units of volume in the brain. The entire brain space is separated into a three-dimensional grid containing small, cubic volumes (termed ‘voxels’, which are compared to ‘pixels’ from a digital 2-dimensional image). The hemodynamic patterns, measured as blood oxygenation changes or Blood Oxygenation Level Dependent (BOLD) signals, have particular features as time from stimulus until peak, height

CHAPTER 1. INTRODUCTION

and width of response peak, area under the curve, among other summary measures that can be used to trace neuronal activation.⁴⁰ Notwithstanding, the information they convey is used as a whole when they are considered continuous functions.

Processes that, conceptually, are produced by continuous functions can be captured by sampling observations that are dense on their given index. In our first example, brain activation within a voxel (represented by the hemodynamic response) is followed in time, usually taking measures every 2 seconds and sampling over periods of minutes. The data, which is usually larger in dimension than traditional longitudinal data, is referred to as ‘functional data’ or ‘intensive longitudinal data’.

Functional data⁴¹ have expanded the way we conceptualize information that is clustered due to temporal or spacial order. Instead of having thirty measures correlated in time, we have one observation coming from a continuous process that is sampled at thirty time points. The correlation is imposed by unknown functional parameters that can be conceptualized and decomposed into a linear combination of known mathematical functions. Models incorporate variability via error terms at each sampled time (that can also be considered measurement error). Given the previous conceptualization, a model for a functional outcome, that is a model for the BOLD activation in a particular voxel for the i th participant (M_i) from time 0 up to time T , can be written as:

$$M_{it} = \alpha_t + \epsilon_{it},$$

for $t \in [0, T]$. In this model, $\{\alpha_t\}_{t=0}^T$ is the average function across participants,

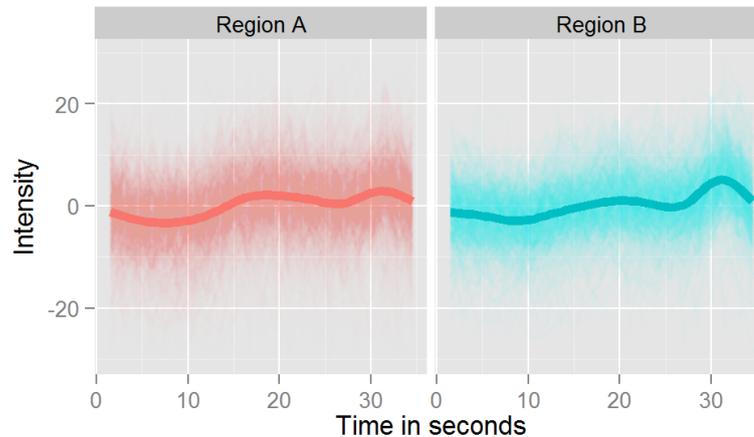


Figure 1.2: Example of functional data: BOLD contrast measured in two brain regions. Region A is the right Anterior Insula, while Region B is the dorsal Anterior Cingulate Cortex.

and deviations from this function are captured by the $\{\epsilon_{it}\}_{t=0}^T$. Typically, the ϵ_{it} are assumed independent and centered around zero for all t and i . Residual correlation of errors can be incorporated through the use of participant-specific random ‘functions’.⁴²

Figure 1.2 shows functional data from the pain study.¹⁴ In this trial, each individual participated in 24 trials under high heat and 24 trials under low heat. Furthermore, the BOLD contrast time series for all voxels was summarized into averages of regions of interest (ROIs). Here, the average BOLD contrast for only two regions (A for the right Anterior Insula, B for the dorsal Anterior Cingulate Cortex) are plotted. The smoothed point-wise mean for each group is plotted by a wider line. This line is our estimate of α .

1.4.1 Functional data models

In order to relate functional data to other information, more complex models are required. Functional data analysis⁴¹ provides tools to analyze functional data. I present a brief introduction classified by the role that the functional variable has in the model.

1.4.1.1 Function-on-scalar regression

In function-on-scalar regression, the functional variable is regressed on scalar covariates. Each scalar covariate has a time-varying effect, and the sum of the effects of all covariates ultimately describes the time-varying correlation in the functional variable. These models are also called ‘time-varying effect models’.⁴³

As an example, we could model the average BOLD response in Region A as:

$$M_{it} = \alpha_{0t} + \alpha_{1t}Z_i + \epsilon_{it},$$

for $t \in [0, T]$. In this model, $\{\alpha_{0t}\}_{t=0}^T$ is the average function for participants that received low heat, while $\{\alpha_{1t}\}_{t=0}^T$ is the observed difference in means between participants under high heat and participants under low heat.

1.4.1.2 Scalar-on-function regression

Also known as functional regression, the scalar-on-function regression relates a scalar outcome to functional covariates. In these models, the effect of the function M on a scalar Y is captured by a weighted integral, where the weights represent the effect of a particular time point of M on Y . Let Y_i be the pain response. We can define the following model to relate the measured BOLD response in Region A to pain response:

$$Y_i = \alpha_0 + \int_0^T \alpha_{1t} M_{it} + \epsilon_i.$$

Here, the effect of Region A on pain, $\{\beta_{1t}\}_1^T$, is a function that takes values on the same time domain as M . This function can characterize how different sections of M are related to Y .

1.4.1.3 Function-on-function regression

Suppose we would like to relate two functions together, like how the average BOLD response in Region B (Y_{it}) is related to the average BOLD response in Region A (M_{is}). We could define a model like the following:

$$Y_{it} = \beta_{0t} + \int_0^t \beta_{ts} M_{is} ds + \epsilon_{it}.$$

CHAPTER 1. INTRODUCTION

This model relates what happens at time t for Region B (Y_{it}) to the history of Region A ($\{M_{is}\}_{s=0}^t$). This is called the 'historical linear model'.⁴⁴

1.4.1.4 Estimation

Estimation of the functional parameters can be done by decomposing the functional observations and parameters into linear combinations of known basis functions - like b-splines, wavelets, or functional principal components, followed by penalized least squares or penalized maximum likelihood.^{41,45-50}

1.5 Overview of the dissertation

This chapter has presented a brief background on the fields of causal inference, causal mediation, measurement error and functional data analysis. In the following three chapters, we address the complications of making causal inferences when there is measurement error in covariates, when there are variables that are functions of time, and when the experimental design is different than the traditional randomized controlled trial. Each chapter proposes new statistical methodology and illustrates it by solving a question in public health or neuroscience.

In Chapter 2, we combine the causal inference framework introduced in section 1.1 with the measurement error framework from section 1.3 to assess the effects of using a mismeasured covariate when designing an observational study with propen-

CHAPTER 1. INTRODUCTION

sity score methods. We illustrate our method by estimating the ATT of living in a disadvantaged neighborhood on adolescent substance use and mental health. In Chapter 3, we extend the causal mediation framework presented in section 1.2 to incorporate functional variables from section 1.4 as mediators and outcomes, and apply it to understand the thermal pain experience and the connection between the right Anterior Insula and the dorsal Anterior Cingulate Cortex under thermal stimuli. In Chapter 4, we frame the within-subject experimental design in terms of potential outcomes, define a new set of assumptions to assess causal mediation, and make use of the previously presented functional mediation models to investigate if the right Anterior Insula mediates thermal pain.

We make final remarks in Chapter 5, connecting the previous three topics and proposing future methodological work, as well as other applications that can advance public health.

Chapter 2

Propensity Score Analysis with Covariate Measurement Error

Propensity score methods are commonly used to estimate causal effects in non-experimental studies, as they help to ensure that treatment and comparison groups are similar with respect to observed covariates.^{8,9} Nearly all existing propensity score methods assume that covariates are measured without error. However, in reality, covariate measurement error may be the rule, not the exception. Self-reported measures, latent variables measured using scales, and disease status definitions comprised of surrogate measures are all examples of variables measured with error. If only the error-prone version of the variable is available, but the assignment mechanism itself used the true covariate, then the true confounder remains unmeasured.

Preliminary investigations have shown that measurement error can have detri-

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

mental effects on the performance of propensity score methods. For example, Steiner *et al.*⁵¹ show that measurement error can degrade the propensity score's ability to reduce bias, although Millimet⁵² shows that the bias is fairly limited if there is relatively little measurement error and if the error itself is not related to treatment group or covariates. McCaffrey *et al.*⁵³ have shown formally that propensity scores based on direct use of error-prone covariates will not yield covariate balance on the underlying true covariate, and thus will not provide accurate treatment effect estimates.

A variety of methods for handling measurement error in regression settings have been developed. These include the method of moments,³⁷ regression calibration,⁵⁴ simulation-extrapolation (SIMEX⁵⁵), and multiple imputation.^{56,57} However, there has been very limited work extending these approaches to causal inference settings using propensity score methods, and the considerations may be quite different. For example, established methods are interested in one specific linear or non-linear model for the outcome, where primary interest is in the coefficients of the variables that are measured with error. Meanwhile, in the propensity score context we care about having a correct propensity score model for the treatment, correct predicted values from this model, and the resulting treatment effect estimates obtained by applying those propensity scores in some way to the outcome analysis. In other words, we care less about how measurement error influences the coefficients on particular variables in a model, and more on how covariate measurement error influences how well we can estimate causal treatment effects.

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

There are just a few papers that do investigate covariate measurement error in propensity score settings. Sturmer *et al.*⁵⁸ consider an error-prone propensity score that is estimated from a model that ignores an important confounder (e.g., the true covariate, in our scenario) and propose a method called “propensity score calibration” to estimate an updated propensity score that accounts for this unobserved confounding. Propensity score calibration uses an approach related to regression calibration and relies on observing the missing confounders on a subset of the original sample and also assumes non-differential error across treatment groups. Meanwhile, McCaffrey *et al.*⁵³ propose a measurement-error bias-corrected inverse probability of treatment weighting estimator. A limitation of both of the Sturmer and McCaffrey approaches is that they assume that the error distribution is the same across treatment groups (i.e., the measurement error is non-differential across groups.) Another approach that addresses covariate imbalance and measurement error is to use a doubly robust method (as in Rotnitzky *et al.*⁵⁹) and apply existing methods for measurement error to the outcome model but not the propensity score model. However, if the predicted propensity scores are incorrect (i.e., if the measurement error is not accounted for in the propensity score estimation), this would detract from the benefits of using propensity score methods.

Therefore, extensions of existing approaches that account for measurement error when using propensity score methods are needed. In the present work we investigate one such extension. We consider a scenario in which a calibration sample is available,

and adapt Multiple Imputation for External Calibration (MI-EC⁵⁷) to correct for covariate measurement error in propensity score estimation and use.

2.1 Propensity scores and the importance of accurate covariate measurement

The propensity score, first introduced by Rosenbaum and Rubin,⁸ is defined as the probability of receiving treatment given the observed covariates. Propensity score methods, such as matching, weighting, or subclassification,⁹ help ensure that the treatment and control groups being compared are as similar as possible on the observed characteristics, and they often yield more reliable estimates of treatment effects than do traditional methods such as regression adjustment (e.g., see Martens *et al.*¹⁰).

We consider the problem of estimating the average treatment effect on an outcome Y , where the treatment assignment T ($T \in \{0, 1\}$) and the outcome Y are affected by a set of confounders (X, Z) . First, we define a potential outcome $Y_i(t)$ as the outcome that we would observe if person i receives treatment t . With two treatments (control and treatment) there are two potential outcomes: $Y_i(0)$, the potential outcome if person i receives the control condition, and $Y_i(1)$, the potential outcome if person i receives the treatment. The average treatment effect is a comparison of these potential outcomes, such as $\Delta = E[Y_i(1) - Y_i(0)]$.

We assume that if we assign treatment t to person i we observe their potential

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

outcome for treatment t (the consistency assumption, $[Y_i | T_i = t] = Y_i(t)$; for a discussion on the topic see Cole and Frangakis⁵). We also assume that the assigned treatment of one person does not influence the potential outcomes of another one, and that each treatment has only one version, known as the stable unit treatment value assumption (SUTVA⁶⁰).

We focus on non-experimental study designs, in which we assume strong ignorability of the treatment assignment.⁸ We assume 1) that each person has a positive probability of getting either treatment – called the positivity assumption, where $P(Z_i = z | X_i, Z_i) > 0 \quad \forall z$, and 2) that the treatment assignment is independent of the potential outcomes, given a set of observed covariates X, Z : that is, $T_i \perp\!\!\!\perp Y_i(1), Y_i(0) | X_i, Z_i$.

Given that the outcome Y is also influenced by the confounders X, Z , we would like to find groups of people that only differed by which treatment T they received, and did not differ in any other way. Since finding people with the same levels of all possible confounders is difficult in practice, a summary measure that also balances the distribution of confounders across treatment groups is helpful. The propensity score is such a balancing score and creating groups with similar propensity scores makes the distribution of X and Z similar across groups. As noted, there are different methods that use the propensity score to achieve balance across treatment groups.⁹

The balancing property of the propensity score relies on having a correct model for the treatment assignment. To be correct, the model must include all the relevant

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

confounders and must have the correct form. If one confounder is measured with error, the true confounder remains partially unobserved. Let W be a covariate that is correlated highly with X , and thus is essentially a measure of X with more error. If we use W in our propensity score model instead of using X , we would not achieve complete balance on X and our estimates would be subject to confounding.⁵³ Note that regression adjustment that uses W would also be subject to remaining confounding.³⁵

2.1.1 Inverse Probability of Treatment Weighting

Inverse Probability of Treatment Weighting (IPTW) is a method that uses the propensity scores to generate weights that, when used when estimating the treatment effect, result in having similar distributions of covariates among treated and control groups. For this work, we estimate the treatment effect using a weighted difference in sample means between treatment and control groups.

We start by posing a model for the treatment T assignment given the confounders X, Z . This model is only used for generating the predicted propensity scores. This allows us to use methods that are parametric – like generalized linear model with a logistic or probit link, or machine learning algorithms like generalized boosted regression models and classification and regression trees.⁶¹

Let $\hat{p}_i = \hat{P}[T_i = 1 | X_i, Z_i]$ be the predicted propensity score for person i . IPTW generates weights based on the inverse of the probability of treatment assigned, which

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

allows for estimation of the average treatment effect on the whole population (ATE). Let \hat{u}_i be the weight for person i . To estimate the ATE, individuals in the treatment group receive a weight of $\hat{u}_i = \frac{1}{\hat{p}_i}$, whereas individuals in the control group receive a weight of $\hat{u}_i = \frac{1}{1-\hat{p}_i}$. The weights \hat{u}_i generate a pseudo-population in which the distribution of covariates is the same in the treated and control groups, and the weighted difference estimates the average treatment effect Δ . In contrast, we could be interested in the average treatment effect among the treated population (ATT). In this case, the treated population have unit weights ($\hat{u}_i = 1$ if subject i is treated), while the population in the control group are weighted by the odds of being treated ($\hat{u}_i = \frac{\hat{p}_i}{1-\hat{p}_i}$ if subject i is in the control group.)

Note that a linear model on the observed outcome Y that incorporates the correct variables in the correct form (including all non-linearities, and having no measurement error) would estimate Δ correctly, assuming the model for \hat{p}_i is correct. The benefit of using IPTW with covariate adjustment in the outcome model is that this method is doubly robust. It will be unbiased if either (but not necessarily both) the propensity score model or the outcome model is correct.⁵⁹

2.2 Measurement error and propensity score methods

In this paper, we examine the consequences of using a covariate measured with error in the estimation of the average treatment effect using IPTW and we investigate the performance of MI-EC (described in further detail below) in correcting for bias due to this measurement error. We consider a classical measurement error model:

$$W = X + e, \tag{2.1}$$

where X is the true confounder, W is the error-prone covariate, and e has some distribution that does not depend on X nor Y , and has zero mean.³⁵ It is common to assume $e \sim N(0, \sigma^2)$. Given the measurement error model, we can define the reliability of the error-prone covariate X to be $r = \frac{\text{var}(X)}{\text{var}(W)}$.

Our setting relies on two samples (see Figure 2.1). The first is the main study sample, in which we observe the outcome of interest Y , the treatment assignment T , a set of confounders measured without error Z , and W , the version of the true confounder X that is measured with additive error. The second is the calibration sample, where only (X, W) are observed. This set-up is encountered when using measures that are calibrated against gold standards in studies external to the main study.

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

Sample	Observed Data					
	W	X	Z	T	$Y(0)$	$Y(1)$
<i>Calibration</i>	✓	✓				
<i>Main</i>	✓		✓	✓	✓	✓

Figure 2.1: Structure of the data. We focus on a setting in which there are two samples, one that contains external information (the calibration sample, with W and X), and one that contains information for the observational study (the main sample, with W, Z, T, Y). We observe $Y(0)$ for the people in the control group, and $Y(1)$ for the treated group, and the main sample can be much larger than the calibration sample.

A common approach for handling measurement error in general is that of regression calibration.^{35,54} This approach involves defining a regression calibration model and using it to predict X with information from W . However, in the calibration setting, we cannot apply regression calibration in a valid manner to our setting of propensity score estimation. For regression calibration to be valid, all confounders of the X and Y relation must be included in the regression calibration model. Since Z is correlated with X and predicts Y , it should be part of the model. But Z is not in the calibration sample, so a model that only uses X and W is not valid.

We consider two approaches for dealing with covariate measurement error in propensity score estimation: a naive method, and multiple imputation for external calibration (MI-EC).

2.2.1 The naive method

The basic naive method ignores the measurement error and uses the error-prone covariate W , instead of X , in the propensity score model. Specifically, it regresses T on W, Z to estimate the propensity scores. Then, it uses IPTW to get an estimate of the treatment effect Δ .

2.2.2 Multiple imputation for external calibration

Multiple imputation for external calibration (MI-EC;⁵⁷) is an imputation-based approach to handling measurement error. In particular, MI-EC generates multiple imputations of the true covariate, X , in the main sample, using information on the relationship between W and X in the calibration sample, as well as information on Y, T, Z, W from the main sample. It thus generates imputations in a way that is congenial (the imputations use all of the variables used in the analysis model) and reflects the relationships between the covariates, the treatment, and the outcome, yet still corrects for the measurement error.^{62, 63}

MI-EC relies on several assumptions. It assumes that the joint conditional distribution of $(X, Z, T, Y | W)$ is multivariate normal, and that this distribution is the same in both the main and calibration samples, while the distribution of W can vary between them. Furthermore, it assumes that the mean of the joint conditional distribution is linear in W and the covariance matrix is constant. Formally, we state

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

this as:

$$f(Y_i, T_i, Z_i, X_i | W_i) \sim N(\alpha W_i, \Sigma) \quad (2.2)$$

for all i in main and calibration samples.

A common assumption in measurement error models is the non-differential measurement error – also called the standard surrogacy assumption. It is one that assumes that the distribution of W is ignorable once we condition on the true covariate X and other helpful covariates, and it is formally stated as $f(Y | X, T, Z, W) = f(Y | X, T, Z)$. In contrast, MI-EC assumes a stronger version of this, in which the distribution of Y, T, Z does not depend on W once we condition on a value of X :

$$f(Y, T, Z | X, W) = f(Y, T, Z | X). \quad (2.3)$$

As pointed out by Liao *et al.*,⁶⁴ this assumption can be regarded as the common non-differential measurement error assumption requiring also that the measurement error is independent of Z and T given X (having $f(W | X, T, Z) = f(W | X)$). It implies that we assume that the amount and structure of the measurement error do not vary across levels of treatment T , levels of the final outcome Y , or across levels of the rest of the covariates Z .

Applying MI-EC to propensity score methods poses possible violations to the required assumptions. Assumption (2.2) is immediately violated because the treatment

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

variable is binary, but Guo *et al.*⁵⁷ show that this violation does not impact the correction of bias and non-coverage of confidence intervals (and we further investigate this in the simulations described below). Meanwhile, assumption (2.3) may be violated when a covariate is measured differently between the treated and the control group, or when the error grows with respect to a covariate only measured in the main sample. See section 2.5 for more discussion on this topic.

Given assumptions (2.2) and (2.3), we can construct the posterior distribution $f(X | Z, T, Y, W)$. These assumptions are used in identification of the joint distribution $f(X, Z, T, Y | W)$ using the two samples, as we never observe (T, Y, Z, W, X) for any individual; we either observe $f(T, Y, Z | W)$ or $f(X | W)$. They further allow us to relate all five variables using linear regression coefficients and covariances. We then use these to construct a posterior distribution using the SWEEP operator.^{57,65}

Guo *et al.*⁵⁷ use Reiter's⁶⁶ two-stage imputation procedure, in which they draw m sets of parameters from the posterior distribution, then for each set, produce n samples of X . The method makes $m \times n$ predictions of X , which can be used in standard methods of analysis and the results combined using combining rules in.⁶⁶

In this paper we pair the MI-EC method with propensity score weighting with the goal of estimating $\Delta = E[Y_i(1) - Y_i(0)]$, the marginal average causal effect. A benefit of the MI-EC approach is that once X is multiply imputed, any propensity score approach (e.g., IPTW, matching, or subclassification) could be used. Similarly, a “doubly robust” approach that uses the covariates in both the propensity score

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

and outcome models can also easily be used. The steps for applying MI-EC with propensity score methods are the following:

1. obtain nested imputations of the true covariate X using MI-EC;
2. for each imputation, calculate the propensity scores;
3. for each imputation, apply any propensity score method (we use IPTW) and obtain an estimated treatment effect $\hat{\Delta}^{(m,n)}$; and
4. use Reiter's combining rules to get the final estimate and confidence interval.

2.3 Simulation Study

Guo *et al.*⁵⁷ present simulations that show the performance of MI-EC when estimating parameters in a linear model. We extend the simulations conducted by⁵⁷ to include a binary treatment variable and its effect Δ , a model for the treatment assignment, propensity score estimation, and a model for the outcome. We use the simulation study to compare the bias, root mean square error, and confidence interval coverage of four methods. Code to implement these methods, as well as to conduct the simulation, is available in an online appendix (http://ywebbvar.github.io/PS_MIEC/).

2.3.1 Methods compared

We compared the methods described in section 2.2:

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

1. The naive method
2. The “true” method, using the true covariate X
3. Uncongenial MI-EC, which used $f(X | W, Z)$ (uncongenial because it does not include variables that are subsequently included in the treatment effect estimation⁶²)
4. Congenial MI-EC, which used $f(X | W, Z, T, Y)$

For the MI-EC methods, we used $m = 12$ draws from the parameter distribution and $n = 3$ samples for each m , following Guo *et al.*⁵⁷

2.3.2 Data Generation - Normally distributed simulation

We use two samples, the main sample and the external calibration sample. We are interested in the effect of a treatment T on an a univariate, continuous outcome Y . However, the treatment assignment, as well as the outcome, depend on univariate confounding variables X and Z . Meanwhile, X is correlated with Z , and is measured with error as W . In the main sample, the vector (Y, T, Z, W) is observed, whereas in the external calibration sample, the vector (X, W) is observed.

The treatment values are assigned according to the following logistic regression model,

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

$$\log \left(\frac{P[T = 1 | X, Z]}{1 - P[T = 1 | X, Z]} \right) = \gamma_0 + \gamma_X X + \gamma_Z Z, \quad (2.4)$$

where γ_X and γ_Z are the average change in log odds of receiving the treatment for a unit increase in X or Z , respectively. We generate X and Z to follow a multivariate normal distribution as:

$$f(X, Z) \sim N_2 \left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right\}, \quad (2.5)$$

we use the following classical measurement error model:

$$f(W | T, X, Z) \sim N(X, \sigma^2), \quad (2.6)$$

and we define the distribution of the potential outcomes as:

$$f(Y(T) | T, X, Z) \sim N(\Delta T + \delta_X X + \delta_Z Z, \tau^2), \quad (2.7)$$

where the errors of the potential outcomes $Y(1), Y(0)$ are independent, and with equal variance.

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

	Parameter	Value		Parameter	Value
	N_{sim}	1500	W	low r	0.3
	n_{calib}	500		moderate r	0.6
	n_{main}	2500		high r	0.9
				very high r	0.999
T	γ_0	0			
	γ_Z	0.4	Y	Δ	2
	small γ_X	0.4		δ_X	0.5
	large γ_X	1.2		δ_Z	0.1
				τ^2	1
(X, Z)	low ρ	0.3			
	medium ρ	0.6			
	high ρ	0.9			

Table 2.1: Values of parameters used in simulations. N_{sim} is the number of simulations, n_{calib} is the number of observations in the calibration sample, and n_{main} is the number in the main sample. The rest of the parameters appear in the propensity score model in (2.4), the model for X and Z in (2.5), the measurement error model in (2.6), and the outcome model in (2.7).

We considered three levels of correlation ρ between the missing covariate X and the other confounder measured without error Z . We also used two levels of association between the confounder X and the treatment assignment, expressed as γ_X . Finally, we varied the variance of W to achieve four levels of reliability r . The specific values used in the simulation are presented in Table 2.1.

We ran 1500 simulations for every combination of level of correlation ρ , level of association γ_X , and reliability r . In each simulation we: generated 2500 observations for the main sample and 500 for the calibration sample; we applied the different methods to impute the missing covariate X ; and for each method, we used Inverse Probability of Treatment Weighted (IPTW) estimation for the average treatment

effect.

We examined the performance of each method for estimating the average treatment effect. In particular, for each method we generated the estimated difference in outcomes between treatment and control groups, calculated with inverse probability of treatment weights. We then calculated, for each of the methods, the bias, root mean squared error, and the percentage of simulations in which the 95% confidence interval covered the true effect.

2.3.3 Data Generation - Non-normally distributed simulation

To assess sensitivity of the methods to some of the assumptions of MI-EC we also simulated settings in which either $Y(t)$ and/or X had a skewed distribution. For X , we defined $X_1 \sim F_{(200,100)}$, $X_2 \sim \chi_1^2$, and $X_3 \sim N(0, 1)$. Then, we defined the variable X as a linear combination of X_1, X_2, X_3 , truncated at 4. We used a method based on principal components⁶⁷ to generate a variable Z with a predefined correlation with X . For the potential outcomes $Y(t)$, we defined an error ϵ as the linear combination of $\epsilon_1 \sim F_{(300,20)}$ and $\epsilon_2 \sim \Gamma(2, 2)$, and the potential outcomes as $Y(t) = \Delta T + \delta_X X, \delta_Z Z + \epsilon$. We ran simulations with:

1. $Y(t)$ coming from a normal distribution and X coming from a skewed distribution,

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

2. X coming from a normal distribution and $Y(t)$ coming from a skewed distribution,
3. both X and $Y(t)$ coming from skewed distributions.

2.3.4 Results

2.3.4.1 Normally-distributed simulation

Results from the normally-distributed simulation studies appear in Figure 2.2. In summary, as expected, a naive method that simply uses the covariate measured with error leads to bias in the treatment effect estimate across settings with less than perfect reliability. Another approach that uses only the joint distribution of the true covariate and the error-prone covariate to multiply impute the true covariate, termed ‘uncongenial MI-EC method’, also leads to bias. In contrast, the congenial MI-EC method, which incorporates both the observed outcome and the treatment assignment in the imputation, estimates the treatment effect almost as well as if the true covariate were available in the main data set.

As expected, there is substantial bias in the treatment effect estimate when using the covariate measured with error in the propensity score model (the naive method). This bias decreases as the reliability of the covariate increases. A reliability of 30% of the error-prone covariate can lead to bias in the treatment effect estimate that amounts to 0.3 standard deviation units (compared to $\Delta = 2$, it represents 15% of

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

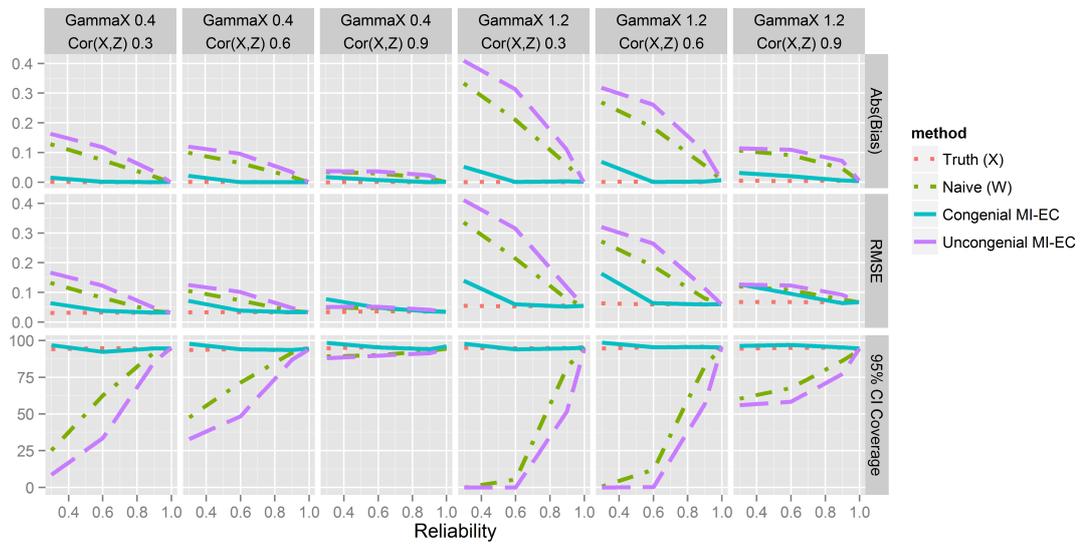


Figure 2.2: Results from the normally-distributed simulation comparing the proposed congenial MI-EC method with the truth, the naive approach, and the uncongenial MI-EC. Increasing reliabilities of W are shown in the horizontal axes, while absolute bias (first row), root mean squared error (second row), and coverage of a 95% confidence interval (third row) for Δ are shown in the vertical axes. Columns define different levels of confounding – small confounding when the effect of X on treatment assignment (GammaX) is 0.4, and large confounding when it is 1.2; as well as different levels of correlation between the unobserved X and the observed Z ($\text{Cor}(X, Z)$).

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

the treatment effect.) We found that the bias does not depend on the magnitude of Δ . Larger confounding by X (measured by its effect on the treatment assignment T) increases the bias in the estimate of Δ . Furthermore, a stronger correlation between X and Z reduces the bias. When the reliability is low and the association of X on T is large, the bias under low correlation between X and Z is about 0.3 units; meanwhile, if there is high correlation, the bias is about 0.1 standard deviation unit. Finally, the bias for the naive method increases with an increasing association of the error-prone covariate X on the treatment assignment T (γ_X), and it is scaled by the size of γ_X .

The uncongenial MI-EC approach that uses only the joint distribution of X and W to impute the true covariate X leads to bias greater than that of the naive method. Compared to the naive method, the bias ranges from a 7% increase under strong correlation between X and Z , to a 118% increase when there is low correlation between X and Z , and there is low reliability. In contrast, the congenial MI-EC method (which includes both the observed outcome and the treatment assignment in the imputation) estimates the treatment effect almost as well as if the true covariate X were available in the main data set. It decreases the bias by 85% in the worst-case scenario, when there is poor reliability, poor correlation between X and Z , and a large effect of X on the treatment assignment. In such a setting, the total bias of the congenial MI-EC method is 0.05.

The root mean squared error (RMSE) results are similar to those for bias. One exception is that the RMSE of the congenial MI-EC method is larger than that of

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

the naive method under mild conditions of measurement error (under poor reliability, small confounding effect of X and large correlation of Z and X , located on the second row and third column.) This is due to the increase in variance from the imputation procedure. However, when there is a larger confounding effect of X , the RMSE of the the congenial MI-EC method is equal to or smaller than that of the naive method.

With regards to coverage, the MI-EC method yields 95% Wald confidence intervals with a coverage around 95% under all simulation scenarios. Under low reliability, the MI-EC method provides coverage of about 97%, leading to a small loss of power; meanwhile the naive method can have coverage of 25% under low reliability and small confounding, or 0% under low reliability and large confounding. Meanwhile, when there is high correlation between X and Z , the coverage of the naive method improves. It is about 80% when there is low confounding, and 60% under high confounding. Therefore, even when the bias in the treatment effect estimate is not very large for the naive method, the confidence intervals do not provide 95% coverage.

2.3.4.2 Non-normally-distributed simulation

Results under violations of the joint normality assumption for (Y, X, Z) are similar, indicating that the MI-EC approach is not particularly sensitive to the assumption of multivariate normality. When only Y is misspecified (as binary, or as a highly skewed bimodal truncated continuous variable), while X, Z, W come from a joint normal distribution, the previous results hold. Whereas if X, Z , and W follow a

highly skewed bimodal truncated continuous distribution, while Y follows either a binary, normal or skewed distribution, the magnitude of the bias increases for all methods, although the relative ranking of methods, and the general preference for the congenial MI-EC method, remains. Full details are provided in the e-appendix (available at http://ywebbvar.github.io/PS_MIEC/).

2.4 Illustrative Example

2.4.1 Overview and set-up

We now apply the MI-EC method to actual data, estimating the effect of living in a disadvantaged neighborhood on past-year substance use and mental health outcomes among adolescents using the National Comorbidity Survey Replication Adolescent Supplement (NCS-A). The NCS-A is a nationally representative survey of U.S. adolescent mental health (N=10,123), the methods and prevalence estimates of which have been described previously.⁶⁸⁻⁷⁰ Participating adolescents gave informed assent and their parents or guardians gave informed consent. The Human Subjects Committees of Harvard Medical School and the University of Michigan approved recruitment and assent/consent procedures. Neighborhood disadvantage was defined using an established scale⁷¹ that has been used previously in several epidemiological studies (e.g., Roux *et al.*⁷²). Neighborhoods were classified as disadvantaged if they were in the lower tertile of the scale scores, as done in Rudolph *et al.*⁴ We consider

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

two outcomes: 1) past-year substance (alcohol or drug) abuse or dependence, and 2) past-year anxiety or depressive disorder. These outcomes correspond to Diagnostic Statistical Manual IV (DSM-IV) diagnoses.⁷³ Because previous research suggests that the relationship between living in a disadvantaged neighborhood and mental health may differ by urbanicity,⁴ we restrict our analysis to the subset of NCS-A participants living in urban areas.

Maternal age at the birth of the adolescent is an important confounder of neighborhood – adolescent health associations, because it serves as a measure of family socioeconomic status. Ideally, maternal age at birth would be reported by the mother. For this example, we consider the mother’s report of her age at the birth of the adolescent the true confounder, X . However, it is not always feasible to conduct interviews of both adolescents and their parents, so this confounder is frequently reported by the adolescent. We consider the adolescent’s report of maternal age at birth as W , a mismeasured version of X . For the purposes of this illustration, we restrict the urban subset of the NCS-A to those who have both X and W ($n=1,926$), as this allows us to use the true estimate (using X) as a reference.

The propensity score model includes gender, current age of the adolescent, race/ethnicity, region of the country, family income, family structure (i.e., the adolescent living her/his whole life with her/his mother and/or father), and maternal age at birth as main effects. We estimate the average effect of neighborhood disadvantage on prevalent substance abuse/dependence and prevalent anxiety and depression among

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

those who currently live in disadvantaged neighborhoods (the average treatment effect on the treated, ATT), controlling for confounding through ATT weights (weighting by the odds). These disorders are considered prevalent if they were present in the 12 months prior to the diagnostic interview. For this illustrative example, we ignore the survey sampling design and weights and interpret the resulting effect estimates as the effect in the sample of adolescents in the NCS-A. However, the imputed values of X could be used in a survey design-based, weighted analysis to generate nationally representative estimates.⁷⁴

We divide the NCS-A sample into a calibration and study sample by randomly sampling 400 participants to use as the calibration sample and drop X from the remaining 1,526 to use as the study sample. As expected, adolescent-reported maternal age at birth is a noisier version of the mother-reported variable (the adolescent-reported variable has variance of 32.0 and the mother-reported variable has variance of 30.7 in the calibration sample). However, the two variables are highly correlated (0.94). Due to this high correlation, we add additional classical measurement error to adolescent-reported maternal age at birth to make two noisier versions of W . We compare the true (using mother-reported maternal age at birth, X), naive (using adolescent-reported maternal age at birth, W), congenial MI-EC (including the outcome, Y , exposure of living in a disadvantaged neighborhood, T , and vector of covariates, \mathbf{Z}) and uncongenial MI-EC (including T , \mathbf{Z} but not Y) estimates of the ATT for three X, W correlation scenarios: 1) the true correlation, 0.94, 2) noisier measure-

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

ment error with correlation 0.72, and 3) noisiest measurement error with correlation 0.30. As in the simulation, we use $m = 12$ draws from the posterior distribution and $n = 3$ imputations for each m .

2.4.2 NCS-A Results

Figure 2.3 shows the estimated ATT of living in a disadvantaged neighborhood on adolescent prevalent drug or alcohol abuse or dependence disorder and prevalent anxiety or depressive disorder. Specifically, the effect on the y-axis is the risk difference associated with living in a disadvantaged versus nondisadvantaged neighborhood for those who live in disadvantaged neighborhoods.

As seen in Figure 2.3, the effect estimates are slightly biased when the mismeasured version of maternal age at birth is used as if it were the truth. For example, naively using the version of adolescent-reported maternal age at birth with the most measurement error (correlation=0.30) would result in an estimate of the effect of living in a disadvantaged neighborhood on prevalent alcohol or drug abuse/dependence that is biased towards the null (-0.014 versus -0.016), and would result in an estimate of the effect of living in a disadvantaged neighborhood on prevalent anxiety or depression that is biased away from the null (0.082 versus 0.056). Although using the mismeasured covariate would not change inferences in the case of prevalent alcohol or drug use, in the case of prevalent anxiety or depression, using the version of adolescent-reported maternal age at birth with the most measurement error would

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

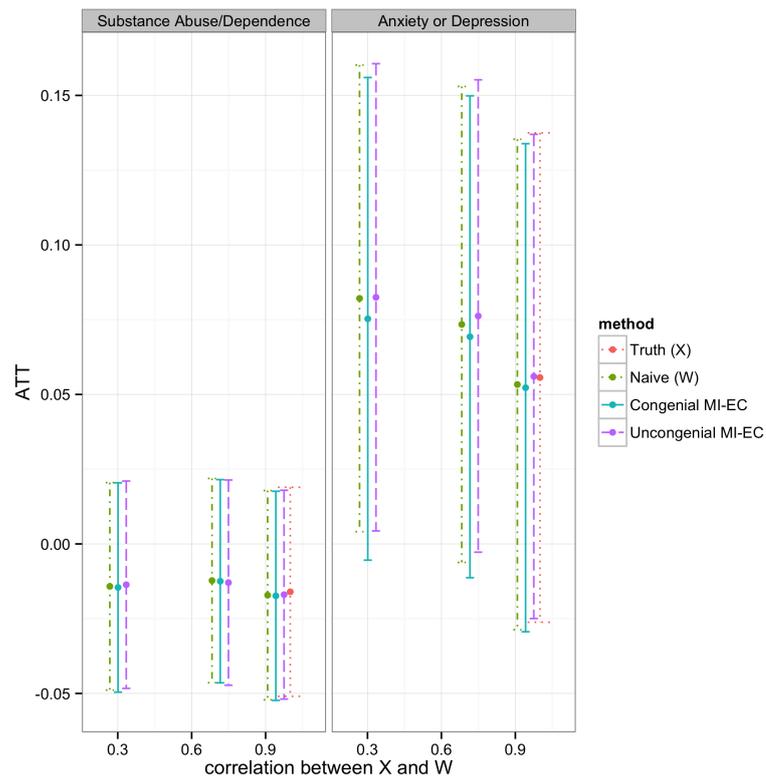


Figure 2.3: Results from illustrative example. ATT estimates and 95% confidence intervals comparing the proposed MI-EC method with the truth, the naive approach, and the uncongenial MI-EC for each of 3 X, W correlation scenarios. Estimates are for the average effect of living in a disadvantaged neighborhood on risk of having a current 1) substance abuse dependence disorder and 2) anxiety or depressive disorder for those who live in disadvantaged neighborhoods.

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

result in a type-1 error—that is, we would conclude that the ATT is statistically significant when it is not.

We note that this example is used for illustrative purposes—substantive conclusions should not be drawn for several reasons. First, we are using a subset of urban NCS-A participants who have both maternal-reported and adolescent-reported maternal age at birth variables, which is not a meaningful population about which to draw inferences. Second, we are not incorporating the survey design and weights into this simple illustration. While we are using the sandwich estimator to calculate standard errors, it is not modified to incorporate the survey weights, sampling strata and clustering by neighborhood. Third, more complex models than what we fit here (e.g., including additional noncontinuous covariates) resulted in convergence problems with the current implementation of MI-EC. This is an area for future work. Fourth, positivity violations (cases where the probability of living in a disadvantaged or nondisadvantaged neighborhood is very small given some vector of covariate values) is frequently a concern when estimating neighborhood effects, but for this illustrative example, we have not addressed this issue.

2.5 Discussion and Conclusion

In the present work, we found that using a covariate measured with error in a propensity score method can lead to bias in the estimated treatment effect. How-

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

ever, a congenial MI-EC approach that includes the outcome, the treatment, and all confounders in the imputation model can be used to help correct for measurement error-induced bias.

The importance of congeniality has been discussed previously in the broader multiple imputation literature.^{62,63} If a variable is used in the analysis procedure, it must be included in the imputation model for the approach to be congenial. If such a variable is absent, it implies that the absent variable is independent of the joint distribution defined in the imputation model.

On a similar note, Liao *et al.*⁶⁴ discussed how regression calibration, which can be regarded as a single imputation method, requires the inclusion of all confounders in the regression calibration model. Cefalu and Dominici⁷⁵ have shown an example of this result. In their case, they had a mismeasured exposure, a set of confounders, and an outcome. They found that unless the model used to predict the exposure included all confounders from the outcome model, the estimate of the exposure effect was biased. This speaks to having a congenial imputation model, but does not consider including the outcome or the treatment in the joint distribution from which to “impute”. A limitation of the MI-EC approach is that the need to use the outcome in the imputation violates the separation of “design” from “analysis” that is important in the broader propensity score literature and should be done with caution.⁷⁶ Future work should investigate the costs of incorporating the outcome, and consider ways that concerns in utilizing the outcome could be addressed.

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

The MI-EC method by Guo et al. assumes a joint multivariate normal distribution. It is assumed because it makes it easier to construct a posterior distribution for the missing X when only two pieces available -the main and calibration samples - are available, using summary measures of $f(Y, Z | W)$ and $f(X | W)$. In their simulations, they showed that their method is robust to a binary Z or a mildly skewed X . On this note, Liao *et al.*⁶⁴ commented on the necessity of this assumption, since the multiple imputation method can be compared with a Monte Carlo integration of the distribution $f(Y, T, X, Z | W)$, over the observed data, which does not require assuming the joint multivariate normal distribution. Meanwhile, if an internal validation sample were available, one could use more flexible Bayesian methods for multiple imputation to construct $f(X | Y, T, Z, W)$.

The joint multivariate normal assumption is automatically violated in our case, because T is binary. Yet, the MI-EC method performs well, and it was also robust to having non-normal distributions for Y . However, we did observe convergence problems when we included many binary observed confounders, which may be due to a more extreme violation of the joint multivariate normal distribution assumption.

Finally, we have assumed W comes from a classical measurement error model, and that the error is non-differential with respect to treatment groups, and non-differential with respect to baseline covariates. The first assumption can partially be relaxed, as the MI-EC method can handle a measurement error model that is linear in X . However, because the calibration sample only includes information on X and

CHAPTER 2. PROPENSITY SCORE ANALYSIS WITH COVARIATE MEASUREMENT ERROR

W , the measurement error model must be strongly non-differential.⁵⁷ By strongly non-differential, we mean that we assume that the measurement error distribution is the same for all levels of Y , Z and T (this last requirement represents a measurement error that is non-differential with respect to treatment groups, similarly to Sturmer and McCaffrey's methods.) Extensions of this work include: relaxing the assumption of a non-differential measurement model and comparing the performance of other propensity score methods using MI-EC.

In conclusion, we demonstrate that using a propensity score to control for confounding that is estimated as function of covariates measured with error leads to biased estimates of the treatment effect. However, when a calibration data set is available, MI-EC can be used to help correct for such bias.

Chapter 3

Functional Mediation Analysis

3.1 Introduction

Mediation analysis has become a standard tool in almost all aspects of psychological science. It allows researchers to investigate the role of intermediate variables that lie on the path between an independent variable and a dependent variable, and has been used extensively to explain many important questions in modern psychology research. In clinical psychology, Arnstein *et al.*⁷⁷ found that the relationship between pain intensity and depression in patients with chronic pain can be partially explained by the effect pain intensity has on their sense of self-efficacy. In marketing psychology, Sherman *et al.*⁷⁸ studied how consumer's emotions respond to store environment, and impact purchase behavior. In organizational psychology, Liden *et al.*⁷⁹ examined how work satisfaction is explained by the characteristics of the job at hand through their

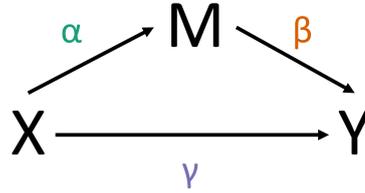


Figure 3.1: Simple path model. The independent variable X presumably affects the dependent variable Y , both by having a direct effect and an indirect effect mediated by M .

effect on sense of empowerment. In neuropsychology, Atlas *et al.*⁸⁰ discovered areas in the pain processing network that mediate the different pain experiences that are induced by expectations.

To illustrate, consider the simple path model shown in Figure 3.1. When the effect of the independent variable X on the dependent variable Y is at least partially directed through the intervening variable M , then M is said to be a mediator. In mediation analysis one typically distinguishes between three types of effects: direct, indirect and total effects. The direct effect is the influence of one variable on another that is unmediated by any other variable in the model. The indirect effect of a variable is the influence mediated by at least one intervening variable. Finally, the total effect is the sum of the direct and indirect effects.

The influence of the intermediate variable on the dependent variable is frequently ascertained using structural equation models, with the model coefficients interpreted as effects. In a highly influential article, Baron and Kenny (1986) proposed a frame-

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

work for performing mediation using a system of linear equations. It is based on fitting a series of three regressions that model how X affects M , X affects Y ; and X and M together affect Y . After estimating the parameters of this model, one can use it to quantify the direct, indirect and total effects.

Though it has found wide usage, in order to use this framework it is necessary that each of the measurements of X , M and Y be univariate scalar variables¹. However, in many situations this may not be reasonable or practical. A recent example involves the use of brain imaging to study the relationship between a painful thermal stimulus and self-reported pain (Wager et al., 2008). In this experiment a noxious heat stimuli was applied at one of two different levels (low/high) to each of 20 subjects. In response, subjects were asked to provide subjective pain ratings roughly 14 seconds following the offset of the stimulus. While the experiment was being performed brain activity was measured using functional magnetic resonance imaging (fMRI). The goal was to find brain regions whose activity acted as potential mediators of the relationship between heat level and pain rating. Placing this experiment into the standard mediation framework, we can let X represent the stimuli (i.e., applied heat level), the variable Y represent the reported pain and the variable M represent the brain response. Here both Z and Y are scalar, while the brain response consists of time series data. In this setting, standard mediation techniques are only applicable if the mediating time course is summarized as a single scalar response, such as peak amplitude or area

¹While extensions have been made to accommodate multiple mediators,⁸¹⁻⁸⁴ existing methods require them to be scalar variables.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

under the curve. However, the brain response is not necessarily well described by a single summary measure and, in addition, such a measure provides no temporal information about the relationship between X and Y . Therefore, in this setting it would be beneficial to extend the mediation framework to allow the variable M to use information across the entire response; something currently not possible in standard mediation models.

In this work we consider the same simple three-variable path model described in Fig. 3.1, with the novel feature that one or more of the variables can be considered continuous functions of time. We denote this new approach *functional mediation analysis*. It provides an extension of current mediation analysis techniques to the functional data analysis (FDA) setting (Ramsay and Silverman, 2005). Conceptually, functional data are thought of as sample paths of a continuous time stochastic process. Although the observed trajectories are often rough and fluctuating, in many applications of FDA there is scientific reason to believe that the true underlying response is smooth in time. The setting where the intermediate variable M is treated as a continuous function (see Fig. 3.2A for the analogous path diagram) was previously discussed in Lindquist (2012). A benefit of this approach is that it allows us to not only test whether brain responses are directly or indirectly related to behavioral and physiological outcomes, but also provide valuable information about the timing of this relationship. Here we provide extensions of that approach as well as discuss situations where other variables are functions.

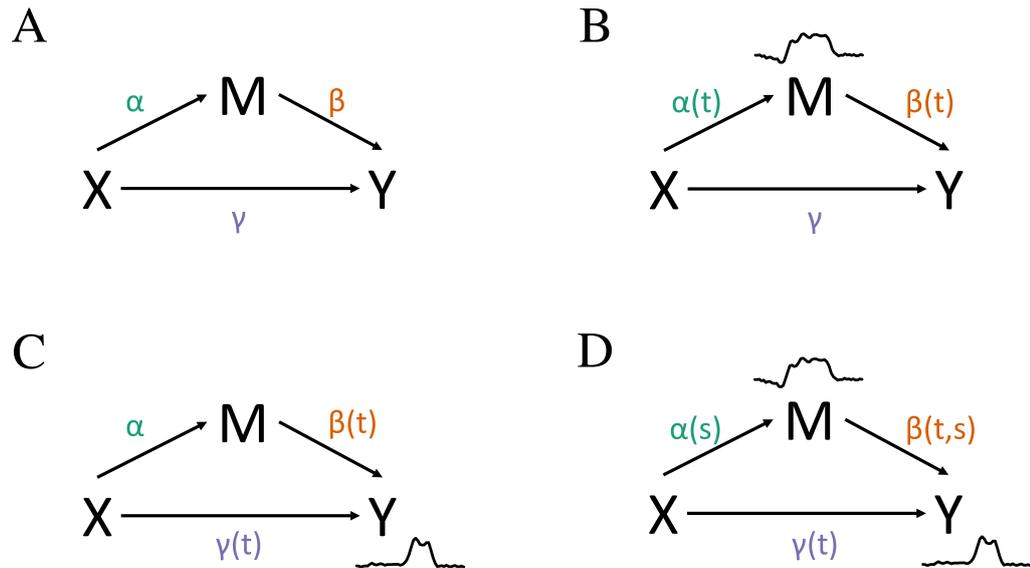


Figure 3.2: Functional mediation models, where an independent variable X presumably affects a dependent variable Y , directly and through M . Figure 2A depicts the traditional Scalar X - Scalar M - Scalar Y path model. Figure 2B depicts the Scalar X - Functional M - Scalar Y mediation model described by Lindquist.¹⁴ In this model, X has a functional effect on M , while M has a functional effect on Y and X has a scalar effect on Y . Figure 2C depicts the Scalar X - Scalar M - Functional Y model. Here, the effects of X and M on Y are functional, while the effect of X on M is scalar. Figure 2D depicts the Scalar X - Functional M - Functional Y model. In this model, the effect that X has on M , the effect that M has on Y , and the effect that X has on Y are all functions. The effect of M on Y is a two-dimensional function.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

Though the proposed method is described in the brain imaging setting, it has clear applications in other areas of psychological research, like those pertaining to ecological momentary assessments (EMA, for a review, see Shiffman *et al.*⁸⁵). EMA capture behavioral data in real time through the use of physiological sensors,⁸⁶ wearable computing,⁸⁷ electronic diaries,^{88,89} and handheld devices.^{90,91} They sample at periodic intervals or at random times, obtaining detailed information for either short or long periods of time. The models we present allow the study of mediators of the impact of interventions on behavior through time, and also to assess how behavioral changes mediate the response to other outcomes.

The chapter is set up as follows. We begin by discussing the Baron and Kenny (B-K) approach towards mediation in section 3.2. Next, we introduce various functional extensions of the B-K approach in section 3.3. Then we discuss how to estimate and perform inference using the new approach in sections 3.4 and 3.5. We illustrate the methods' efficacy using simulation studies in section 3.6, and in two applications in pain psychology (sections 3.7 and 3.8). We finalize with a discussion of the methods in section 3.9.

3.2 Mediation Analysis

In the standard approach toward mediation analysis, the variables X , Y and M all take univariate scalar values. Consider that the relationship between the variables

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

are modelled using a simple path model, such as the one in Figure 1. In this work, we consider simple recursive three-variable structural equation models of the form:

$$M_i = \delta_1 + \alpha X_i + \epsilon_i \quad (3.1)$$

$$Y_i = \delta_2 + \gamma X_i + \beta M_i + \eta_i. \quad (3.2)$$

for $i = 1 \dots N$.

Using this formulation, it is straight forward to show^{17,19,82} that the total effect of X on Y can be decomposed as follows:

$$\tau = \gamma + \alpha\beta. \quad (3.3)$$

Here γ represents the direct effect of Z on Y , while $\alpha\beta$ represents the indirect (mediated) effect. To demonstrate mediation one can perform a hypothesis test to determine whether $\alpha\beta$ is significantly different from 0. In this setting, a positive mediator is one involved in a pathway that has a net positive effect on the outcome, while a negative mediator has a net negative effect. A statistical test of $\alpha\beta$ is commonly performed using the Sobel test¹⁵ or the bootstrap procedure.⁹²

3.3 Functional Mediation Analysis

In what follows we will discuss three different functional mediation models. The first allows the intermediate variable to be a function and is equivalent to the model discussed in Lindquist (2012). The second allows the dependent variable to be a function. The third allows both the intermediate and dependent variable to be functional. In the following sections we formulate each of these models.

Scalar-Function-Scalar Model

Suppose we are studying a simple recursive three-variable structural equation model where two variables, X and Y , are scalars, while the mediating variable $M(t)$ is a continuous function; see Figure 2A for an illustration. Note that here t represents that the variable/coefficient is a function of t . Also, we write $\mathbf{M} = \{M(t)|t \in [0, 1]\}$ to state that the mediator occurs in the range $[0, 1]$. In our motivating example, X is the treatment assignment, Y is the reported pain, and $M(t)$ is a time series of brain data following each stimulation (that will be treated as samples from a continuous underlying function). Let τ represent the total effect of X on Y and γ the direct relationship (controlling for \mathbf{M}). The path coefficients $\alpha(t)$ and $\beta(t)$ are functions that describe the time-varying relationship between the variables.

A great deal of research has been directed at extending linear models to the functional setting.^{45,46,49,50,93} Currently, techniques exist for performing regression where both/either the response and explanatory variables are functional rather than scalar.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

Using these techniques, the relationships between the three variables can now be expressed in an equivalent system of equations as those shown in (1) and (2). However, since M is now a continuous function, we must use functional linear regression models (Ramsay and Silverman, 2005) instead of standard regression models. Mediation can be assessed using recursive *functional* linear structural equation models of the form

$$M_i(t) = \delta_1(t) + \alpha(t)X_i + \epsilon_i(t) \quad (3.4)$$

$$Y_i = \delta_2 + \gamma X_i + \int \beta(t)M_i(t) dt + \eta_i. \quad (3.5)$$

where $t \in [0, 1]$.

In this formulation, it is easy to show that the total effect of X on Y is given by

$$\tau = \gamma + \int \alpha(t)\beta(t) dt. \quad (3.6)$$

Hence, $\int \alpha(t)\beta(t) dt$ represents the indirect effect. Mediation can be tested by determining whether the integral is significantly different from zero. In addition, the product $\alpha(t)\beta(t)$ provides a functional decomposition of the indirect effects that provides the ability to find specific intervals of time driving the mediation. Therefore, the proposed framework provides the opportunity to access the effects of *functional mediation*.

Scalar-Scalar-Function Model

Suppose we are studying a simple recursive three-variable structural equation model where two variables, X and M , are scalars, while the dependent variable $Y(t)$ is a continuous function; see Figure 2B for an illustration.

$$M_i = \delta_1 + \alpha X_i + \epsilon_i, \quad (3.7)$$

$$Y_i(t) = \delta_2(t) + \gamma(t)X_i + \beta(t)M_i + \eta_i(t). \quad (3.8)$$

where $t \in [0, 1]$.

In this formulation, it is easy to show that the total effect of X on Y is given by

$$\tau(t) = \gamma(t) + \alpha\beta(t). \quad (3.9)$$

for all $t \in [0, 1]$. Given that the total effect varies across the entire range of t , there are direct and indirect effects defined at each time point. It follows that the direct effect at time t is $\gamma(t)$, capturing the effect of the treatment for a fixed level of the mediator; while the indirect effect at time t is $\alpha\beta(t)$. The indirect effect captures the effect of the mediator on the outcome and the effect of the treatment on the mediator. Mediation is tested by determining if the product $\alpha\beta(t)$ is different from zero for some t .

Scalar-Function-Function Model

Suppose we are studying a simple recursive three-variable structural equation model where X is scalars, while both $M(t)$ and $Y(t)$ are continuous functions; see Figure 2C for an illustration.

$$M_i(t) = \delta_1(t) + \alpha(t)X_i + \epsilon_i(t), \quad (3.10)$$

$$Y_i(t) = \delta_2(t) + \gamma(t)X_i + \int_0^t \beta(t, s)M_i(s) ds + \eta_i(t). \quad (3.11)$$

In this formulation, it is easy to show that the total effect of X on Y is given by

$$\tau(t) = \gamma(t) + \int_0^t \alpha(s)\beta(t, s) ds. \quad (3.12)$$

for all $t \in [0, 1]$. Similarly to the scalar-scalar-function case, the three effects - the total, direct, and indirect - are defined for every time point of Y . In this case, $\gamma(t)$ represents the direct effect at time t , while $\int_0^t \alpha(s)\beta(t, s) ds$ represents the indirect effect. Mediation can be tested by determining whether the integral is different from zero for some t . Furthermore, the surface $\alpha(s)\beta(t, s)$ provides a functional decomposition of the mediated effects that can highlight time bands at which mediation is taking place.

3.4 Estimation

The functional mediation models described in the previous section require the estimation of scalar and functional parameters. This can be accomplished through the use of functional data analysis (FDA, Ramsay and Silverman, 2005). Functional data models are used when the regressors or the response are functions of time, and a variety of methods have been developed for their estimation. In terms of notation, data in which the response is a function of time can also be called ‘intensive-longitudinal data’, and⁴³ have written a nice introduction to their analysis.

In functional mediation we require different types of FDA. Models that include scalar regressors and functional outcomes, like the outcome model in eq. 3.8 or the mediator models in eqs. 3.4 and 3.10, are referred as ‘function-on-scalar regression’ or ‘time-varying effect models’.⁴³ Meanwhile, models that include functional regressors and scalar outcomes, like the outcome model in eq. 3.5, are referred as ‘scalar-on-function regression’ or ‘functional regression’. Lastly, models that include functional regressors and a functional response, like the outcome model in eq. 3.11, are referred to as ‘function-on-function regression’.

Estimation of functional models typically involves two steps: regularization and estimation. In the regularization step, the functional variable is decomposed into a combination of known functions. The functional variable can be projected onto a space defined by known basis functions, like b-splines,^{41,45,46,94} or wavelets,^{47,48} or, it can be reduced to a combination of a few principal components.^{49,50} Regularization

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

thus help reduce the dimensionality of the functional variable by constructing the functional variable using a finite number of coefficients and a finite number of known basis or principal components. Then, the estimation procedure can use the basis set or principal components as building blocks for the functional parameter. One can impose smoothness in either the regularization step, by penalizing the smoothness of the projection,^{45,46} or in the estimation step, by penalizing the coefficients towards creating a straight line.^{41,45,49,50} The amount of penalization is determined by a parameter, which is assumed to be known. Many of these methods use cross-validation techniques to choose the smoothing parameter.^{43,50,95,96}

We use the following methods for estimation. ‘Function-on-scalar regressions’, which are regressions with a longitudinal outcome, were estimated using a two-step procedure that first fits linear models at each time point and then penalizes the coefficients via local polynomial smoothing.⁹³ ‘Scalar-on-function’ and ‘function-on-function’ regressions were estimated using functional generalized additive models (fGAMs).^{96,97} fGAMs decompose the functional regressor into splines and penalize the decomposition using random effects. For model 3.5, we used quartic p-splines⁹⁴ with second derivative penalty, whereas for model 3.11 we used tensor product smooths based on cubic p-splines with marginal first difference penalties. Code for fitting scalar-function-scalar, scalar-scalar-function, and scalar-function-function is provided in the online appendix and available through Github.

3.5 Inference

Once the parameters of the functional mediation models have been estimated, we can perform inference on the indirect effect. In mediation analysis we are particularly interested in determining whether the total effect is stronger than the direct relationship controlling for \mathbf{M} .

Testing the significance of the indirect effect can proceed analogously to the fully scalar setting (Sobel, 1982; Baron and Kenny, 1986), that is, by testing the analogous $\alpha\beta$ products. We use bootstrap methods to perform inference for these, given that the exact distribution of the functional estimators and their products is unknown. Our bootstrap method is equivalent to that in Shrout and Bolger (2002) - the case bootstrap. The case bootstrap is a non-parametric bootstrap that samples the entire information from each subject; Shrout and Bolger constructed bootstrap samples by sampling cases $\{X_i, M_i, Y_i\}$. This type of bootstrap has been shown to be superior for inference in linear mixed effect models,⁹⁸ which are at the core of the functional generalized additive models that we use in estimation.

We propose the use of the case bootstrap to test whether the integral or the product is different from zero at each time point. To construct the bootstrap distribution of the product estimators, we proceed as follows:

1. Randomly select individuals to include in the bootstrap sample. Sample with replacement n subject indexes i from the sequence $1, \dots, n$.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

2. Construct the bootstrap sample by gathering the entire information for each subject i that was selected in step 1. For subjects that are included more than once in the bootstrap sample, include their entries as many time as required. In the case of the scalar-function-scalar model, the entire information for subject i is $\{X_i, \mathbf{M}_i, Y_i\}$; for the scalar-scalar-function model, it is $\{X_i, M_i, \mathbf{Y}_i\}$; and for the scalar-function-function model, it is $\{X_i, \mathbf{M}_i, \mathbf{Y}_i\}$.
3. Fit mediator and outcome models. For scalar-function-scalar mediation (models 3.4 and 3.5), record $\int_0^1 \hat{\alpha}(t)\hat{\beta}(t) dt$ and $\hat{\alpha}(t)\hat{\beta}(t)$. For scalar-scalar function mediation (models 3.7 and 3.8), record $\hat{\alpha}\hat{\beta}(t)$. For scalar-function-function mediation (models 3.10 and 3.11), record $\int_0^t \hat{\alpha}(s)\hat{\beta}(t, s) ds$ and $\hat{\alpha}(s)\hat{\beta}(t, s)$. These are the estimators of the indirect effect and its time-decomposition.
4. Repeat steps 1 through 3 a total of B (e.g. 1,000) times.

We proceed to test whether the estimate of the indirect effect (or its time-decomposition) is different from zero. Let $R_0(\cdot)$ be the estimate observed with the original sample (which can be a scalar or a function of one or two time indices), and $R_b(\cdot)$ be the estimate observed at the b th bootstrap sample. For each time point, we compute the bootstrap p-value as:

$$p_{boot}(\cdot) = \frac{2}{B} \min \left(\sum_{b=1}^B I [R_b(\cdot) < 2R_0(\cdot)], \sum_{b=1}^B I [R_b(\cdot) > 2R_0(\cdot)] \right) \quad (3.13)$$

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

In order to account for testing significance at every timepoint t , we correct the bootstrap p-values using the Benjamini-Hochberg procedure⁹⁹ to control for the false discovery rate (FDR). We prefer FDR methods to methods that control the family-wise error rate (FWER) because they allow for positive correlation of p-values across timepoints, which is expected given the assumption that the coefficient functions are smooth. In contrast, it is difficult to incorporate correlation when establishing an appropriate threshold level for the FWER.¹⁰⁰

3.5.1 Causal interpretations

Assumptions are required in order to interpret the parameters as causal mediation effects. First, we assume that the models are correct and there is no interaction between the treatment and the mediator on the outcome (linearity of effects). Second, we assume that the treatment assignment behaves as if it had been randomized (i.e. there are no variables that are causally influencing the treatment and the mediator, or the treatment and the outcome). Third, we assume that the mediator behaves as if it were randomly assigned (there are no variables that influence the mediator and the outcome). A final assumption is that there are no variables that are themselves affected by the treatment and that affect both the mediator and the outcome. More details are provided in the appendix.

3.6 Simulation Study

In this section we present the results of a simulation study designed to compare the false positive rate and the power of different estimators for indirect effects in the three functional mediation models in section 3.3. We performed simulations similar to the scalar-function-scalar model simulations presented in Lindquist,¹⁴ and extended them to the scalar-scalar-function and scalar-function-function models. In total we evaluate four scenarios. The first three scenarios represent cases in which no individual shows an indirect effect, while the fourth scenario represents a case in which every person experiences an indirect effect.

Simulation Scenarios

We start with a sample size (N) of 20 participants, and simulate random Bernoulli draws to assign the treatment, where the probability of getting the treatment condition is $P(Z_i = 1) = 0.5$. We then generate values of M_i and Y_i according to the three models described previously (scalar-function-scalar, scalar-scalar-function and scalar-function-function models) and under four different simulation scenarios.

The simulation scenarios portray three null cases - where the indirect effect is zero or a null function, and one mediation case - where the indirect effect is non-zero or a non-null function. In the first scenario, α and β are null (they equal zero for scalar mediators, and zero at all time points for functional mediators). In the second scenario, α is non-null, while β is null. In the third, α is null while β is non-null.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

Finally, the fourth scenario has α and β as non-null. In all simulations, we construct functional parameters using 30 b-spline bases of order 6 and a set of predetermined coefficients. Our functions are sampled at 40 time points.

Scalar-Function-Scalar Mediation

The simulation for the scalar-function-scalar mediation case is as follows. We begin with the model in eq. (3.4). For δ_1 , the sixth to tenth coefficients are taken at random from a uniform distribution $[-2, 0]$, the following ten are drawn from a $Unif[0, 2]$, and the first five and last ten coefficients are set to zero. For $\alpha(t)$, the tenth to twentieth coefficients are random uniform variables in the interval $[1, 4]$, while the rest are zero. Finally, we simulated error terms $e_i(t)$ for all time points and all participants from a standard normal distribution. Meanwhile, the outcome was simulated based on the model in eq. 3.5. We chose $\delta_2 = 5$ as the intercept, and $\gamma = 2$ as the direct effect of the treatment on the outcome. The $\beta(t)$ function is built with five coefficients taken from a $Unif[2, 10]$ uniform distribution, and is zero elsewhere. Finally, we generated an error η_i from a normal distribution with zero mean and standard deviation 0.1.

Figure 3.3 shows the estimates of path specific parameters in the scalar-function-scalar mediation model, under the four simulations scenarios. Here, α , β and the indirect effect $\alpha\beta$ are all functions of time, while the direct effect γ is a scalar. Simulations 1 through 3 present cases in which there is no mediated effect, and all estimates

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

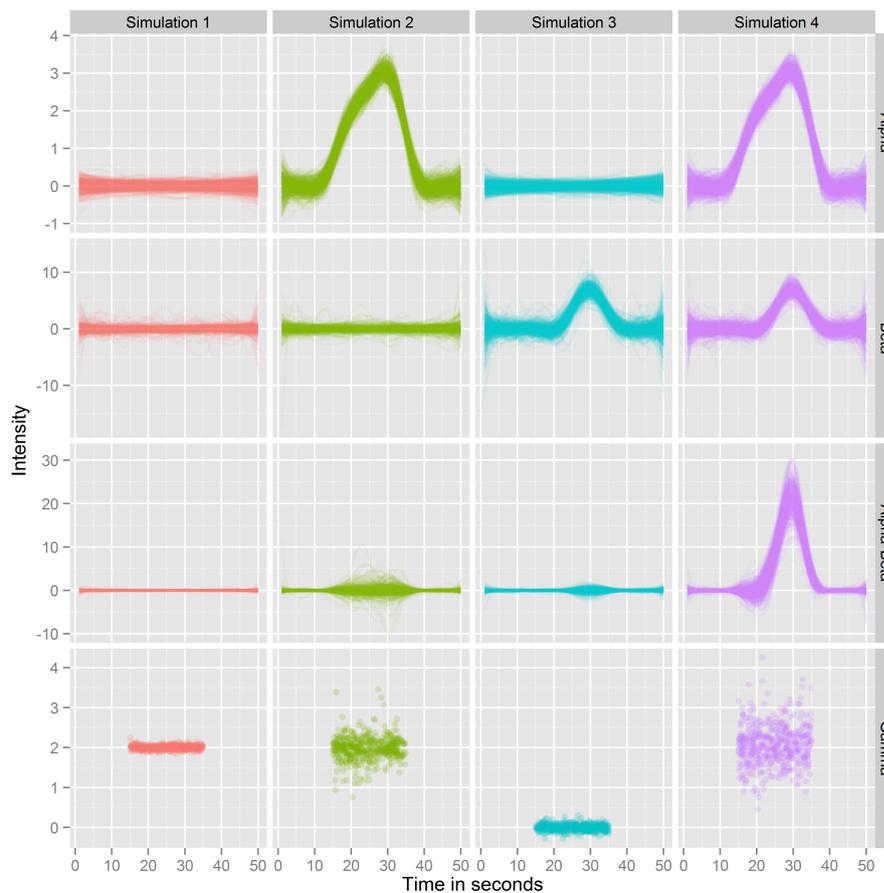


Figure 3.3: Estimates for parameters in scalar-function-scalar mediation models simulated under the four scenarios. Simulations 1 through 3 represent cases in which there is no mediation (the indirect effect $\alpha\beta$ is a null function), while simulation 4 represents a case in which mediation is present.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

are consistent for the null function. Meanwhile, in simulation 4, the indirect effect is consistently estimated. The Mean Squared Error of the direct effect γ varies across the simulation scenarios.

Scalar-Scalar-Function Mediation

We constructed the simulation for the scalar-scalar-function mediation case following the models in equations 3.7 and 3.8. In these models, $\delta_1 = 5$ and $\alpha = 3$, while the functional parameter $\beta(t)$ is as described above. The $\gamma(t)$ function uses positive coefficients in terms 12th through 19th, while the $\delta_2(t)$ function has non-zero coefficients in terms 6th through 22nd. The error terms $\epsilon_i(t)$ and $\eta_i(t)$ are taken from a random standard normal distribution.

Results from the four simulations appear in Figure 3.4. In the scalar-scalar-function mediation model, the path specific parameters δ_1 and α are scalar; while the parameters δ_2 , β , the indirect effect $\alpha\beta$, and the direct effect γ are all functions of time. All path specific parameters are consistently estimated, and the variability of the scalar parameter estimates does not change across simulation scenarios.

Scalar-Function-Function Mediation

For the scalar-function-function mediation case, when mediation is present (simulation 4), we generated data as follows. We first simulated functional mediators as was described in the scalar-function-scalar mediation simulation (models in equations

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

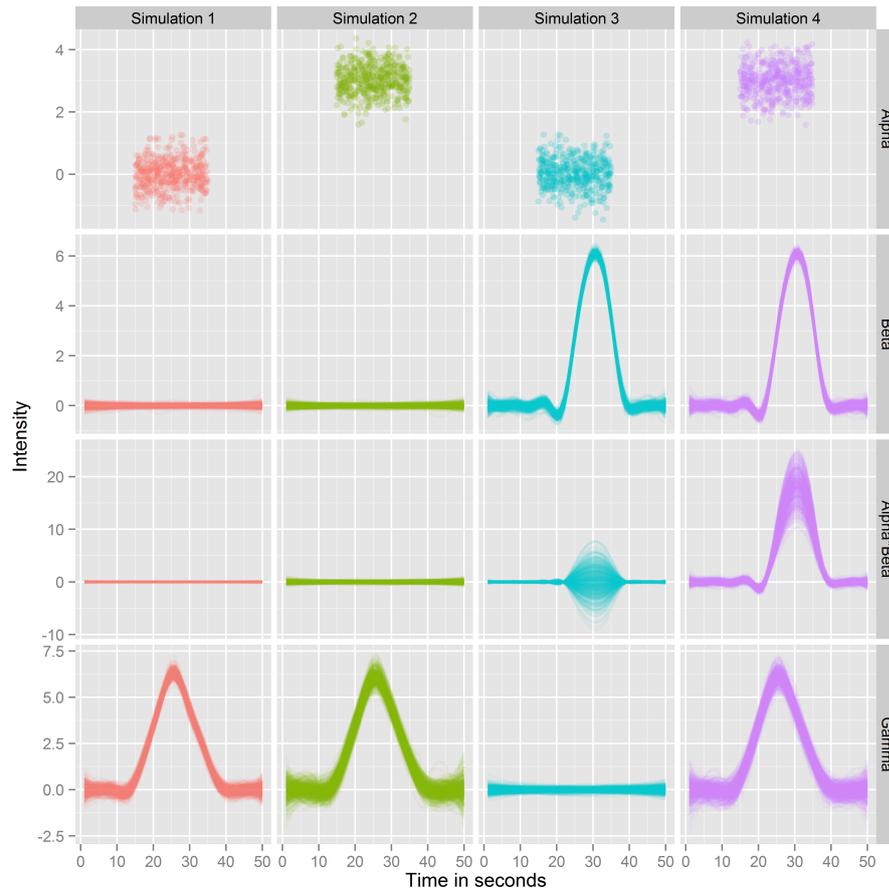


Figure 3.4: Estimates in scalar-scalar-function mediation models simulated under the four scenarios. Cases in which there is no mediation present (simulations 1 through 3) have a null indirect effect ($\alpha\beta$ is the null function), while mediation is present in simulation 4.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

(3.4) and (3.10) are equivalent). We then simulated functional responses using the model in eq. (3.11). In this model, $\delta_2(t)$ and $\gamma(t)$ were generated as described in the scalar-scalar-function model, while the $\beta(t, s)$ was generated in two steps to mimic an effect where only recent activity in the mediator affects the response. We first generated a temporary function of time setting the first fifteen coefficients to zero, the next ten to be sampled from a uniform distribution [6, 8], followed by 5 coefficients sampled from a uniform distribution [2, 3]. We then constructed a lower triangular $\beta(t, s)$ surface by incorporating the latter portion of the temporary function. Finally, we generated errors $\epsilon_i(t)$ and $\eta_i(t)$ from normal distributions with zero mean and standard deviation 1 and 0.1.

Results from these simulations are shown in Figure 3.5. In the scalar-function-function mediation model, all path specific parameters are functions of time. The parameters δ_1 and α are functions of time on the mediator scale (s), while δ_2 , γ and the integrated indirect effect are functions of time on the outcome scale (t). The parameters β and $\alpha\beta$ are functions of both the mediator and outcome time scales. We show cross-sections of the β function for $Y(t = 25)$ and $Y(t = 40)$. The model for $Y(t = 25)$ takes mediator values up to time 24, and weights them using the cross-section of the β coefficient ($\{\beta(s, t = 25)\}_{s=0}^{24}$). All path specific parameters are consistently estimated, and the variability of the scalar parameter estimates does not change across simulation scenarios.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

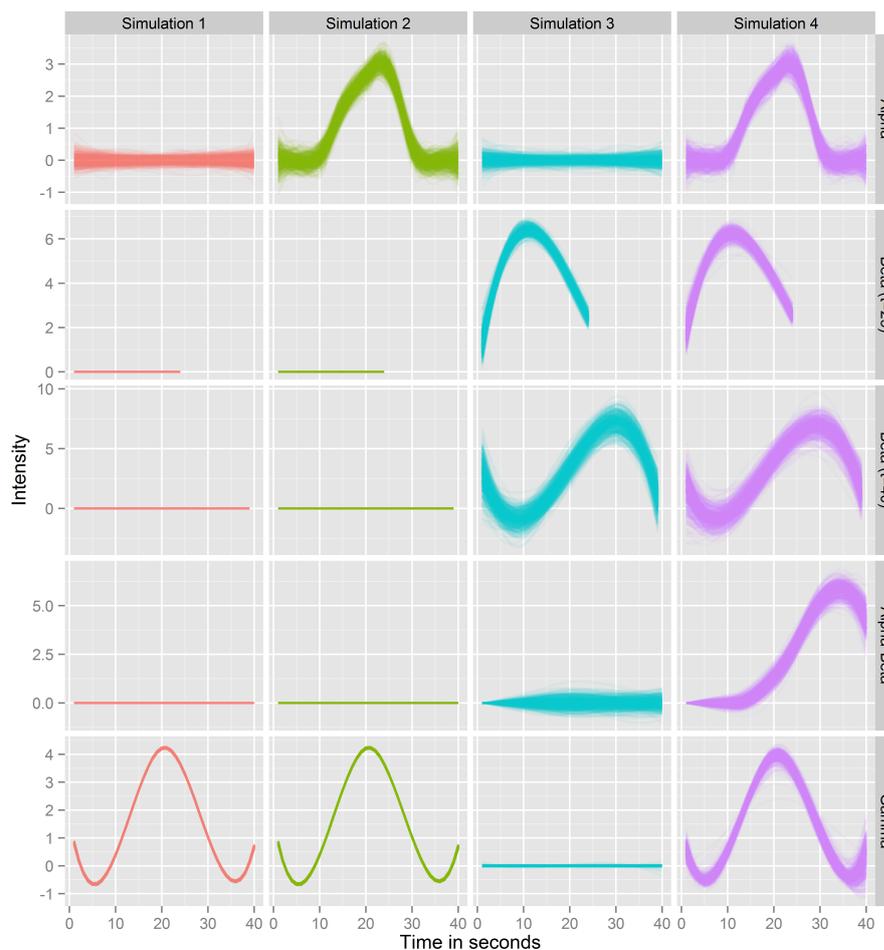


Figure 3.5: Estimates in scalar-function-function mediation models simulated under the four scenarios. Cases in which there is no mediation present (simulations 1 through 3) have a null indirect effect ($\alpha\beta$ is the null function), while mediation is present in simulation 4. We show sections of the β surface at $t = 25$ and $t = 40$.

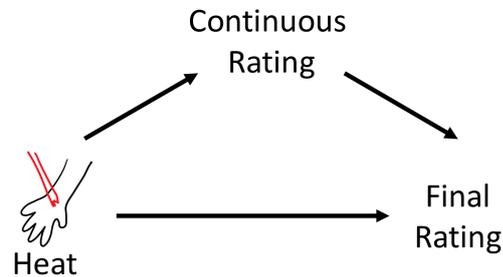


Figure 3.6: Path model for continuous pain rating. The level of heat (maximum of 47, 48, or 49 degrees Celsius) presumably impacts the final pain rating, by having an indirect effect through the continuous pain ratings and a direct effect.

3.7 Data example 1: What part of a continuous pain rating matters most to pain recall?

We now illustrate how scalar-function-scalar mediation can help in determining what time frame is important in pain recollection. A group of 93 participants were stimulated with a noxious heat. A small metal was applied to the arm and its temperature ramped up from room-temperature to 47, 48 or 49 Celsius degrees, then decreased to room temperature. The path diagram is depicted in Figure 3.6.

We fit a scalar-function-scalar mediation model (models (3.4) and (3.5)), and results of estimates and 95% bootstrap intervals are shown in Figures 3.7, 3.8 and 3.9. For the mediator model (3.4), we used the two-step approach to function on scalar regression Fan and Zhang⁹³ described in Section 3.4, and 15 cubic bsplines with

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

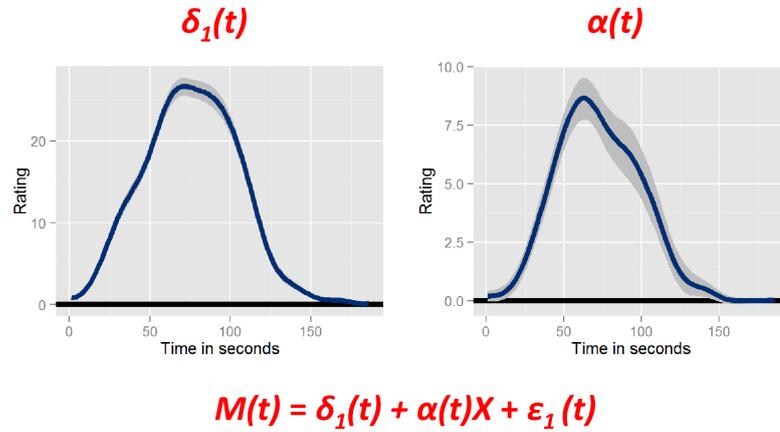


Figure 3.7: Mediator model estimated functions. Time (t) since the beginning of the trial is measured by the x-axis, while the y-axis measures the reported pain rating at a particular t . The function $\delta_1(t)$ represents the average curve when the maximum heat reached 47 degrees Celsius, while the function $\alpha(t)$ represents the effect of increasing the maximum heat by one degree.

second order penalty. For the outcome model (3.5), we used functional generalized additive models⁹⁷ with 15 cubic P-splines with second order penalty.

In the mediator model in eq. (3.4), $\delta_1(t)$ represents the mean pain rating at time t when the maximum temperature reached is 47 degrees Celsius, while $\alpha(t)$ represents the increment that one-degree increase in maximum temperature has on continuous pain rating. In the outcome model, for a fixed level of curve of continuous pain rating, δ_2 (7.13 with 95% BI of 6.31- 7.88) represents the average final pain rating when the maximum heat reaches 47 degrees Celsius, while γ (1.28 with 95% BI 0.84 - 1.63) represents the increase in final pain rating associated with a one-degree increase in maximum heat.

The effect of the continuous pain rating on final pain rating $\beta(t)$, for a fixed level of

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

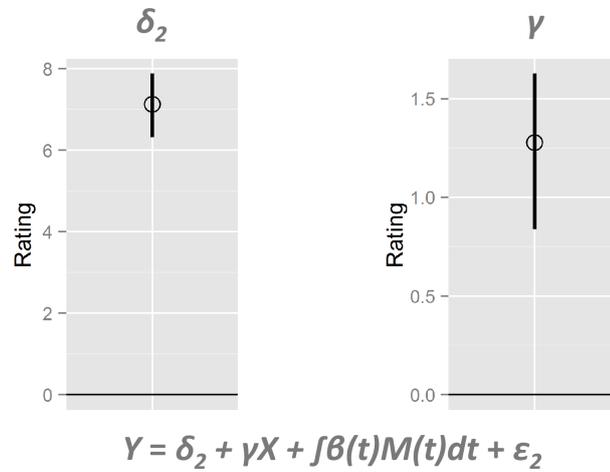


Figure 3.8: Outcome model point estimates. For a fixed level of the continuous pain rating, δ_2 represents the average pain report when the heat reached a maximum of 47 degrees Celsius, and γ represents the effect of increasing the maximum temperature by one unit.

maximum heat, is depicted in Figure 3.9. In general, there is an increase in final pain rating between 50 and 70 seconds, while high continuous pain rating in the beginning or end of the trial decreases the final report of pain. The time decomposition of the indirect effect $\alpha(t)\beta(t)$, is also shown in Figure 3.9. The continuous pain rating between times 40 and 50 seconds is associated with decrease pain ratings, while the continuous rating between 50 and 110 seconds increases the final reported pain.

The summary of the analysis is captured by the direct and indirect effects, depicted in Figure 3.10. The total effect of increasing the maximum heat by one degree on final pain report is divided into a 1.28 increase (95% BI 0.84 - 1.63), while the effect that is associated with the changes the heat had on the continuous pain report accounts for 7.5 units (95% BI 6.7-8.4).

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

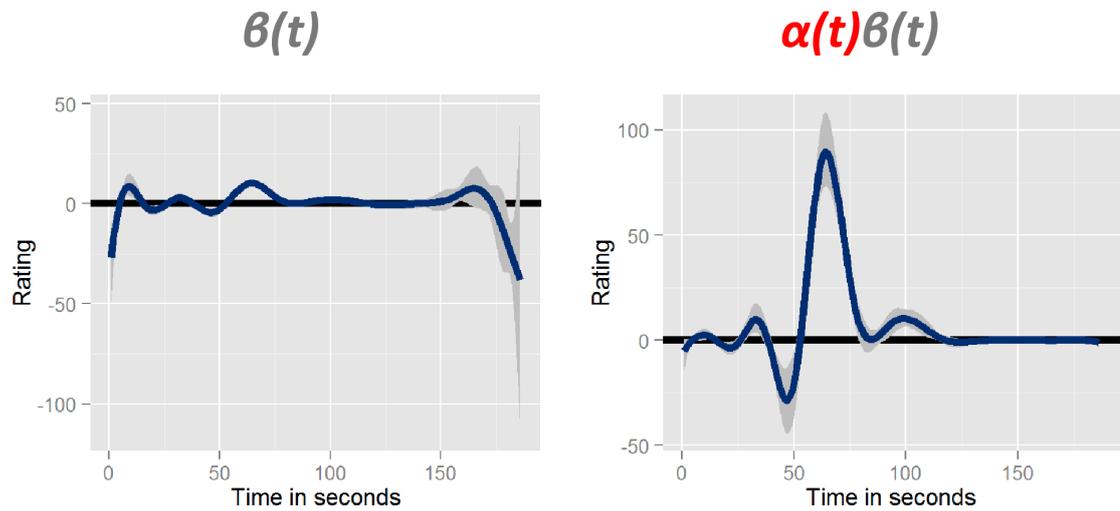


Figure 3.9: Estimated β and $\alpha\beta$ function decomposition for continuous pain rating.

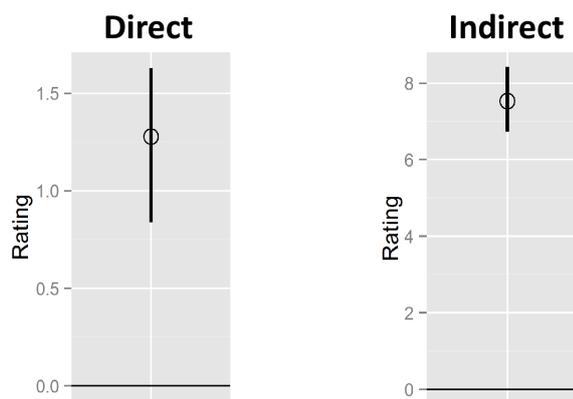


Figure 3.10: Estimated direct and indirect effects for continuous pain rating

3.8 Data example 2: How do different brain regions communicate in response to pain?

In a study of the brain response to thermal pain, 20 subjects (with equal proportions of males and females) received either noxious or non-noxious heat stimuli applied to their forearm while resting in a Magnetic Resonance Imaging (MRI) scanner (Wager et al. 2008). Each trial consisted of 18 seconds of heat application, 14 seconds of rest, 4 seconds for rating the pain on a continuous scale from one to eight, followed by another 10 seconds of rest. Brain activation, as measured by the Blood-Level-Oxygenation-Dependent contrast, was recorded throughout the experiment. To illustrate the scalar-function-function mediation, we focus on the decomposition of the effect of heat on activation in a particular brain region, the dorsal Anterior Cingulate Cortex (dACC), into a direct effect and an indirect effect that is mediated through activation in a second brain region, the right Anterior Insula (rAI). The path model is shown in Figure 3.11. The indirect effect captures the relation between two areas of the brain and is termed ‘functional connectivity’.

We fit scalar-function-function mediation models (3.10) and (3.11). To fit the model in eq. 3.10, we used the two-step approach⁹³ described in section 3.4, and used 15 cubic b-splines with second order penalty to smooth the estimated coefficients. For the function-on-function regression (the model in eq. 3.11), we used functional generalized additive models⁹⁶ mentioned in section 3.4 with the following smoothing

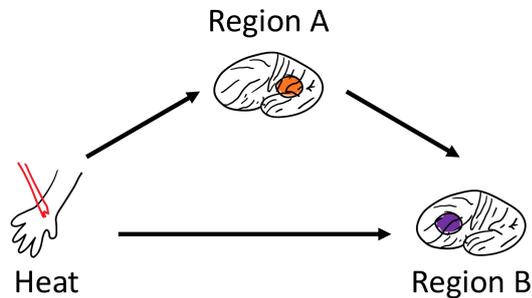


Figure 3.11: Path model for brain connectivity. The level of heat (noxious or non-noxious) presumably affects the activation in brain region dACC, both by having a direct effect and an indirect effect mediated by the activation in brain region rAI.

options: for the functional intercept we used 20 cubic P-splines, for the treatment effect we used 5 cubic P-splines, and for the function-on-function coefficient, we used the tensor product of two sets of 5 cubic P-splines; all used penalties on the second derivatives, and chose penalization parameters using generalized cross-validation.

The estimated path functions, as well as 95% Bootstrap confidence intervals, are depicted in Figures 3.12, 3.13, and 3.14. The overall trajectory of the activation in the rAI, as well as the effect of heat stimulus (path functions $\delta 1(s)$ and $\alpha(s)$ in Figure 3.12) are similar to those of the dACC (path function $\delta 2$). This is interesting given that the latter are not total effects, but estimates for a fixed level of the mediator. That is, holding the activation in the rAI constant, there is a peak in activation in the dACC after 40 seconds and the direct effect of the treatment is a positive increase in activity between 15 and 30 seconds, similar to what is observed in the rAI activation.

The components of the indirect effect are depicted in Figure 3.14. We show cross-sections of the β and $\alpha\beta$ surfaces at selected time points. Figure 3.14.A shows the

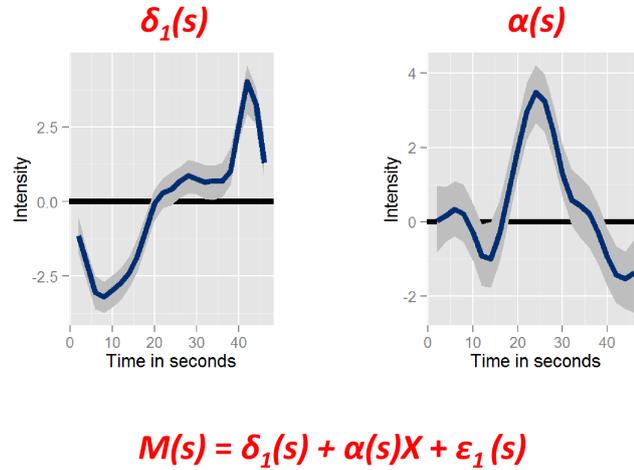


Figure 3.12: Mediator model estimated path coefficients for brain connectivity. Time (s) is measured by the x-axis, while the y-axis measures the BOLD activation at a particular s . The function $\delta_1(s)$ represents the average curve under low heat stimuli, while the function $\alpha(s)$ represents the effect of high heat stimuli.

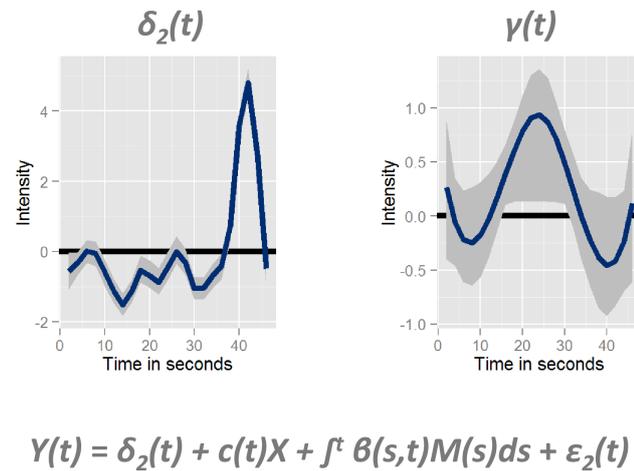


Figure 3.13: Outcome model estimated path coefficients for brain connectivity. For a fixed level activation in the rAI region, $\delta_2(t)$ represents the average activation in the dACC under low heat stimuli, and $\gamma(t)$ represents the effect of high heat stimuli.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

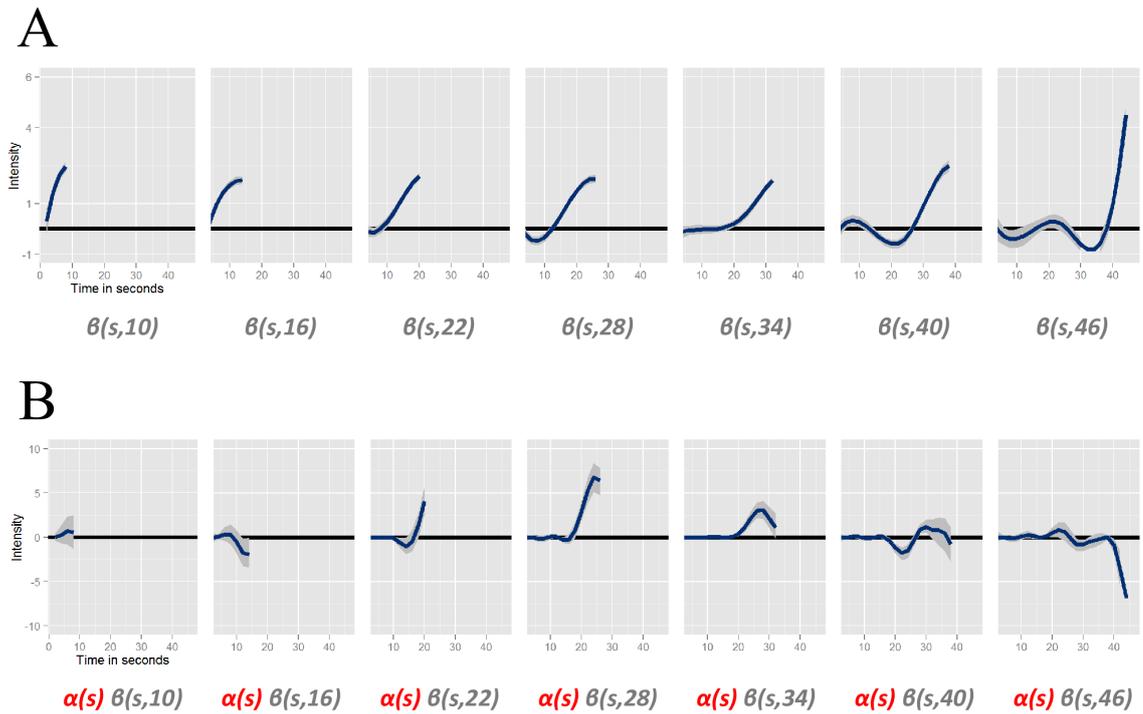


Figure 3.14: Estimated $\beta(s, t)$ and $\alpha(s)\beta(s, t)$ function decomposition for brain connectivity. We show cross-sections at particular t time points for the dACC region. For example in part A, the activation in the dACC region at time 10 can be explained by positive contribution of the first 9 seconds of activation in the rAI region, even after accounting for the effect of high heat stimuli. However, the $\alpha(s)\beta(s, t)$ decomposition shows that there is no indirect effect at time 10.

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

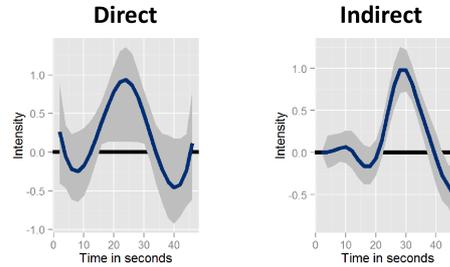


Figure 3.15: Estimated direct and indirect effects for brain connectivity

effect that activation in the rAI has on activation in the dACC region, for a fixed level of treatment ($\beta(s, t)$). That is, among people in the high heat condition, the activation in the dACC at time 10 was explained by changes in activation in the rAI. In particular, a history of high activity in the rAI up to time 9 was associated with high activity in the dACC at time 10. This pattern continued up to time 46, with the activity in the dACC being explained by the latter 10 seconds of activity in the rAI. Meanwhile, the indirect effect time decomposition ($\alpha(s)\beta(s, t)$) is depicted in Figure 3.14.B, where the history of the treatment effect on activation in the rAI has no effect on activation in the dACC at time 10 through 16, then has a positive impact between times 22 through 28, then begins to have no effect or highly negative effect on activation at time 46.

Figure 3.15 shows the estimates of the direct and indirect effects. The direct effect represents the effect of the heat treatment on activation in the dACC that is not associated with making changes in activation in the rAI. This curve is similar to the effect of the heat treatment on activation in the rAI. Whereas the indirect

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

effect shows the cumulative effect that the history of activation in the rAI has on activation in the dACC. Increases in the activation in the dACC between 20 and 40 seconds can be explained by the increases that the heat treatment had on activation in the rAI. In contrast, after 40 seconds, the indirect effect decreases the activation in dACC. We can see that the heat has an effect early on (from 10 to 30 seconds), while the indirect effect appears later in time (from 20 to 40 seconds positively, then after 40 seconds negatively).

The use of scalar-function-function mediation has allowed us to decompose the effect of heat on brain activation into direct and indirect effects that are functions of time.

3.9 Discussion

This article introduces linear functional structural equation modeling as a means of studying time-varying mediation effects, termed ‘functional mediation analysis’. This powerful methodology allows for the discovery of time frames in which a continuous function of time mediates the effect of a treatment, as shown in two data examples. One caveat with functional models is that the number of chosen bases can impact the functional estimates. Generalized cross-validation⁹⁵ was developed to provide a principled way to determine the number of bases, and the methods used in the data analyses in this paper^{96,97} also effectively choose the number of basis

CHAPTER 3. FUNCTIONAL MEDIATION ANALYSIS

using random effects models. Sensitivity analysis can also help in assessing whether changing the number of basis changes dramatically the estimates. Another limitation is that the assumptions for interpreting the mediated effects as causal are very strong. We rely heavily on the structure posed by linear functional models, and we require no confounders of the relations of treatment-mediator, treatment-outcome, and mediator-outcome, to hold at each time point of the functional variables. Further work will incorporate baseline confounders and allow for interactions of treatment and mediator on the outcome.

In terms of applications, the scalar-function-function method allows for the study of functional connectivity, the relation between activity in two areas of the brain. Also, functional mediation methods can serve in the study of diary data in other psychological studies, to investigate the effect that anxiety, depression, or physical activity history have over time.

Chapter 4

Within-Subject Designs for Causal Mediation Analysis

4.1 Introduction

Causal mediation analysis investigates variables that lie in the causal pathway between a treatment and an outcome. In particular, it can separate the effect of an intervention into an effect that is due to changing an intermediate variable - the mediator, and an effect that does not rely upon changing it. The effect of the intervention on the outcome is termed the ‘total effect’, the part of the effect that is due to changing the mediator is a form of an ‘indirect effect’, while the part of the effect that does not rely on the mediator is a form of an ‘direct effect’.

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

Robins and Greenland²³ and Pearl¹⁰¹ defined mediated effects in terms of potential outcomes. However, identification in causal mediation analysis presents a challenge because it often relies on assumptions about the treatment and mediator assignment that cannot be tested. In order to identify causal mediation estimands, we need to assume a form of independence assumption for the assignment of the treatment and mediator with respect to the outcome.^{27,102,103} Since we typically cannot randomize the mediator, we often rely on assuming that the assignment of the mediator is as if it were random when we consider groups defined by the treatment received and observed baseline variables (sequential ignorability as defined in Imai *et al.*²⁷).

Usually, the counterfactual quantity that requires these assumptions to be identified is the outcome that happens if a person is given a particular treatment, but has the mediator level of a different treatment (for example, under the control condition). If the ignorability and sequential ignorability assumptions hold, we can use the observed distribution of mediator values under the control condition to extrapolate to what would happen if those who received the treatment had these mediator values. We do this when we use the mediation formula¹⁰¹ or the non-parametric identification formula.²⁷

In contrast, functional Magnetic Resonance Imaging (fMRI) study designs present a different opportunity. In these studies, it is common to apply different treatments, each with relatively short effects, while a person is inside the MRI scanner. Sobel and Lindquist¹⁰⁴ have defined a framework to study causal effects under this type of

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

experiment, particularly, the causal effect of a scalar treatment on brain activity as measured by an fMRI signal. Within this framework, the order of the treatments applied to each person is either random or fixed (the same order is applied to every person in the trial.) However, this type of design - the within-subject design - has not been explored in the context of causal mediation analysis. These designs can allow for the use of different identifying assumptions to estimate causal mediation effects.

We begin by introducing an fMRI experiment that motivates the present work in Section 4.2. We then present a different set of assumptions that can be used to identify causal mediation effects in a within-subject design of experiments in section 4.3, and propose a method of estimation. We proceed to showcase our method in section 4.4, applying it to the fMRI experiment formerly introduced. We conclude with a discussion of the new assumptions, their use in their application in the fMRI experiment, and final remarks, in section 4.5.

4.2 Thermal Pain Experiment

Consider the experiment presented by Lindquist.¹⁴ The goal of the study was to investigate how the brain processes thermal pain, and it used a design in which each person received multiple treatments at multiple times. This type of design is called the ‘block design’, and is commonly used in neuroimaging studies.^{105, 106}

In this trial, 20 healthy participants received thermal stimuli in their forearm while

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

inside a Magnetic Resonance Imaging (MRI) scanner. A trial consisted of receiving a stimulus (noxious heat or non-noxious heat) for 17 seconds, then a waiting period of 14 seconds, followed by a 4-second period to collect the perceived pain rating by the individual, and a 10-second waiting period. The levels of heat were calibrated individually to evoke low and high pain, and the order in which they appeared was pseudorandom. This procedure was repeated 8 times in every ‘run’, and each subject had 6 runs. In total, there were 48 trials per person. During each run, the participant’s brain activity was measured using the Blood-Oxygenation-Level-Dependent (BOLD) contrast.

The MRI scanner records signals from locations in a three-dimensional grid that divides the brain. Each volume within the grid is called a ‘voxel’. For the purpose of the present work, we focus on the average BOLD response across voxels in one brain region: the right anterior insula. The right anterior insula has been shown to respond to temperature,¹⁰⁷ to thermal pain,¹⁰⁸ and as a possible mediator for thermal pain.¹⁰⁹

Let the application of heat be the treatment of interest, the average BOLD-measured brain activation at the right anterior insula be the mediator, and the expressed pain rating be the outcome. We are interested in the part of the effect that the thermal stimulus has on reported pain that is due to having changed the levels of brain activation at the right anterior insula. This is called the natural indirect effect.¹⁰¹ Quantifying the pain experience will help us understand the experience of pain beyond subjective reports. We will be able to quantify the pain that fibromyalgia

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

The treatment regime assigned to a particular person i is denoted by $\bar{\mathbf{Z}}_{Ti}$, and can differ across participants.

At each time point, there are two processes, one measuring the BOLD activation in the right anterior insula of subject i (the mediator) and one recording the subject's expressed level of pain (the outcome). Let $M_{it}(\bar{\mathbf{z}}_T)$ be the potential true BOLD response at the right anterior insula for person i measured at time t under regime $\bar{\mathbf{z}}_T$. For the outcome, we define $Y_{it}(\bar{\mathbf{z}}_T)$ to be the potential hard outcome for person i at time t corresponding to regime $\bar{\mathbf{z}}_T$.

We summarize the sequences of potential mediators and potential outcomes as $M_i(\bar{\mathbf{z}}_T) = (M_{i1}(\bar{\mathbf{z}}_T), \dots, M_{iT}(\bar{\mathbf{z}}_T))$ and $Y_i(\bar{\mathbf{z}}_T) = (Y_{i1}(\bar{\mathbf{z}}_T), \dots, Y_{iT}(\bar{\mathbf{z}}_T))$, respectively.

4.3.1 Identification of sub-trials

Sobel and Lindquist¹⁰⁴ defined assumptions to identify the causal effect of a treatment regime on an fMRI outcome measured by a time series. In order to assess mediation, we now use modified versions of their assumptions to define the concepts of the effect of the treatment regime on the mediator, and the total effect of the treatment regime on the outcome. Throughout the present work, we assume that there is no interference between participants, and that there is only one version of each treatment regime (the SUTVA assumption across participants⁶⁰). For example, if noxious heat is administered at sub-trials 1, 4, and 15, the amount of heat and the way it is applied does not vary. In the pain trial, the temperature that a participant

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

received as noxious and non-noxious heat was calibrated to their pain tolerance, with low and noxious heat stimuli producing low and maximum tolerable pain. Therefore, the heat stimuli does not vary within subjects, but it does vary across subjects. In order to make population inferences, we may assume that the treatment and control levels for a given person are the levels that are obtained through the calibration procedure, i.e., that the procedure is the same for each person, even if the actual levels differ.

The fMRI signal is known to measure the BOLD response with high levels of error, as considered by Sobel and Lindquist.¹⁰⁴ However, for the purpose of defining causal mediation effects in within-subject designs, we begin by assuming there is **no measurement error in the BOLD signal** (Assumption A1). This assumption states that we could potentially measure the true potential BOLD Response.

We proceed by assuming **temporal consistency** (Assumption A2). This assumption states that the potential mediator levels at time t do not depend on future treatment assignments. Formally, for all $\bar{\mathbf{z}}_T \in \Omega$, where Ω is the set of all possible treatment assignments, the potential mediator and the potential outcome at period t ($M_{it}(\bar{\mathbf{z}}_T)$, and $Y_{it}(\bar{\mathbf{z}}_T)$, respectively), do not depend on stimuli administered after period t . Furthermore, the potential outcomes are assumed to not depend on later potential mediators. Thus, for regimen $\bar{\mathbf{z}}_T \equiv (\bar{\mathbf{z}}_t, \mathbf{z}_{t+1}, \dots, \mathbf{z}_T)$, we can write $M_{it}(\bar{\mathbf{z}}_T) = M_{it}(\bar{\mathbf{z}}_t)$, and $Y_{it}(\bar{\mathbf{z}}_T) = Y_{it}(\bar{\mathbf{z}}_t)$. Temporal consistency can be violated by anticipation reactions (knowing that there will be a particular stimulus along the

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

sequence may create a response at the present time.)

We next assume that there is **control of carry over effects** (Assumption A3). That is, if the potential mediator or outcome depend on past treatments received, they only do so up to P precedent periods. We define the amount of periods for carry over as follows: let $0 \leq P \leq T - 1$ denote the smallest integer such that $\mathbf{z}_{t-P} = \mathbf{z}_{t-P}^*, \dots, \mathbf{z}_t = \mathbf{z}_t^*$ implies $M_{it}(\bar{\mathbf{z}}_t) = M_{it}(\bar{\mathbf{z}}_t^*)$ and $Y_{it}(\bar{\mathbf{z}}_t) = Y_{it}(\bar{\mathbf{z}}_t^*)$ for all $t \geq P + 1$. This assumption allow us to establish the equality of potential mediators and outcomes under two different treatment regimes that have the same treatments in the last P periods.

To illustrate P period control of carry over effects, let's set $S = 2$ treatments, and $T = 12$ total number of periods. We define two treatment regimes:

$$\begin{aligned} \bar{\mathbf{z}}_{12} &= \begin{bmatrix} 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{bmatrix} \\ \bar{\mathbf{z}}_{12}^* &= \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \end{bmatrix} \\ t &= \quad \quad \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \end{aligned}$$

Let $P = 2$. Since $\{\mathbf{z}_t\}_{t=7}^9 = \{\mathbf{z}_t^*\}_{t=7}^9$, then the P period control of carry-over effects assumption (A3) implies $M_{i,9}(\bar{\mathbf{z}}_9) = M_{i,9}(\bar{\mathbf{z}}_9^*)$. Therefore, the carry over effects

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

last for three periods, and the treatments applied prior to those do not affect the current BOLD response. Assumption A3 may be violated when stimuli have effects that do not wash-out.

Furthermore, we assume a form of **no treatment by period interaction for the mediator** (Assumption A4). We assume that, if a treatment regime contains two sections of length P (defined in A3) with the same treatment allocation, the potential mediators at the end of each section share the same distribution. This assumption allows us to formulate the following. For P in (A3) and $P + 1 \leq t < t'$, $\mathbf{z}_{t-P} = \mathbf{z}_{t'-P}, \dots, \mathbf{z}_t = \mathbf{z}_{t'}$ implies $f(M_{it'}(\bar{\mathbf{z}}_{t'})) = f(M_{it}(\bar{\mathbf{z}}_t))$.

The assumption of no treatment by period interaction allows the comparison of two BOLD responses within the same time series. In our last example, the treatment regime $\bar{\mathbf{z}}_9$ contains two similar sections of treatment allocation: $\{\mathbf{z}_t\}_{t=1}^3 = \{\mathbf{z}_t\}_{t=7}^9$, therefore, $f(M_{i,3}(\bar{\mathbf{z}}_3)) = f(M_{i,9}(\bar{\mathbf{z}}_9))$. Assumption A4 can be violated when the order in which the treatments are applied has an effect on the BOLD response. An example is, if the participant gets used to the treatment, the response of a stimulus in latter applications may not be the same as the initial response to such stimulus.

Moreover, we impose an assumption about the design of the experiment: **the potential mediators and outcomes are related solely to one stimulus** (Assumption A5). This implies that the stimuli are separated by at least $Q = P + 1$ units. Additionally, in the pain trial presented in section 4.2, the outcome was collected once after every stimulus. We assume that the time between applying a stimulus and mea-

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

During the outcome must remain constant (R), in order to have the outcomes be comparable across sub-trials.

Given assumptions A1-A5, we define a sub-trial as the application of one stimulus followed by no stimulus in the remaining P periods. Let $\{z_0\}_P$ be a vector of P zeros, then the allocation of treatment s in any sub-trial is defined as:

$$\bar{\mathbf{z}}_s = \begin{bmatrix} z_s & \{z_0\}_P \\ 1 - z_s & \{z_0\}_P \end{bmatrix}.$$

If we consider the noxious heat stimulus as $s = 1$ and non-noxious heat stimulus as $s = 0$, then we can identify trials under noxious heat ($\bar{\mathbf{z}}_1$) and trials under non-noxious heat ($\bar{\mathbf{z}}_0$).

Let j be the index of the sub-trial in a time series. Assumption A5 implies that outcomes are only recorded at times $(j - 1) \times (1 + R)$, therefore, the outcome associated with trial j is $Y_{ij}(\bar{\mathbf{z}}_s) \equiv Y_{i,(j-1) \times (1+R)}(\bar{\mathbf{z}}_s)$. We also define the string of potential mediator values in a trial as $M_{ij}(\bar{\mathbf{z}}_s) = \{M_{it}(\bar{\mathbf{z}}_j)\}_{t=(s-1)}^{(s-1) \times (1+R)}$.

Finally, we assume there is **'no treatment by period interaction for potential outcomes'** (Assumption A6). For example, if a noxious heat stimulus ($s = 1$) is applied at sub-trial j and at sub-trial j' , $\bar{\mathbf{z}}_j = \bar{\mathbf{z}}_{j'} = \bar{\mathbf{z}}_1$, then

$$f(Y_{ij'}(\bar{\mathbf{z}}_{j'})) = f(Y_{ij}(\bar{\mathbf{z}}_j)) \equiv f(Y_{ij}(\bar{\mathbf{z}}_1)),$$

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

defining the distribution of the potential outcomes for person i under noxious heat. Similarly, this assumption defines a distribution under non-noxious heat as well.

The latter distributions allow us to define subject-level causal effects for the contrast of $\bar{\mathbf{z}}_1$ against $\bar{\mathbf{z}}_0$:

$$E_i[M_{ij}(\bar{\mathbf{z}}_1) - M_{ij}(\bar{\mathbf{z}}_0)] \quad \text{and} \quad E_i[Y_{ij}(\bar{\mathbf{z}}_1) - Y_{ij}(\bar{\mathbf{z}}_0)].$$

4.3.2 Identification of causal mediation effects

With assumptions A1 through A6, we are able to identify the distributions for the potential mediators and potential outcomes, $f_M(\{M_{ij}(\bar{\mathbf{z}}_s)\})$ and $f_Y(Y_{ij}(\bar{\mathbf{z}}_s))$, for repeated sub-trials. Given these, we can define the following causal mediation effects for a particular person i :

Within-Subject Natural Indirect Effect $E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_1)) - Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0))]$

Within-Subject Natural Direct Effect $E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0)) - Y_{ij}(\bar{\mathbf{z}}_0, M_{ij}(\bar{\mathbf{z}}_0))]$

Within-Subject Controlled Effect of the Mediator $E_i [Y_{ij}(\bar{\mathbf{z}}_1, m) - Y_{ij}(\bar{\mathbf{z}}_1, m')]$

The within-subject natural indirect effect (ws-NIE) is the average effect that the treatment has on the outcome that is due to changing the levels of the mediator, for participant i . It is the average causal effect for person i contrasting the pain that they report after receiving noxious heat with the pain report that they would report

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

if they had noxious heat, but somehow had the response in the right anterior insula resulting from non-noxious heat. This is the part of the effect of noxious heat that is due to changing the response in the right anterior insula, and tells us how the latter mediates the effect of the treatment. The within-subject natural direct effect (ws-NDE) captures the rest of the treatment effect. It is the average causal effect resulting from the contrast of person i 's pain rating under noxious thermal stimuli that keeps the right anterior insula's response at a non-noxious level against their pain report under non-noxious stimuli. The within-subject controlled effect of the mediator (ws-CEM) represents the causal effect of the mediator on the outcome, unconfounded by the effect of the treatment. That is, the ws-CEM compares the pain reports under noxious stimuli, changing the levels in the right anterior insula by any amount $m' - m$.

We now define assumptions that will allow us to identify the natural effects. Briefly, the usual identifying assumptions for causal effects^{23,27,101,110-112} need to apply only within subjects, with the exception of the constancy assumption.

We start assuming there is **individual ignorability of the treatment assignment** (Assumption B1). That is, for a particular subject, the treatment regime assignment is independent of the potential mediators and potential outcomes. In fMRI studies, the treatment regime is either randomized or it is fixed - that is, the regime is the same for every person. In these situations, this assumption holds.

Next, we assume individual sequential ignorability, or **individual ignorability of the mediator assignment** (Assumption B2). That is, for a particular subject i

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

receiving treatment $\bar{\mathbf{Z}}_s$, the distribution of potential BOLD responses under stimuli s is independent of the potential outcomes $Y_i(z_s, M(z'_s))$. This assumption rules out unobserved confounding of the mediator-outcome relation within a participant, and it would be violated if there are variables that influence the BOLD response as well as the reporting of pain. Personality traits, or other baseline characteristics, would not violate this assumption. Potential violators are characteristics that vary within a person during the experiment. For instance, time since smoking can influence a smoker participant's pain tolerance,^{113,114} although it does not affect subjective pain rating. If it were to influence the way they rate pain, Assumption B2 would be violated. This assumption may potentially be relaxed by requiring it to hold only within levels of the treatment and of covariates measured at the start of the trial, like time.

We further make the **consistency** assumption (Assumption B3). We assume that, if treatment $\bar{\mathbf{z}}_s$ is administered at sub-trial j , we observe the potential mediator and potential outcome associated with it. That is, $M_{ij}^{obs} = M_{ij}(\bar{\mathbf{z}}_s)$ and $Y_{ij}^{obs} = Y_{ij}(\bar{\mathbf{z}}_s, M_{ij}(\bar{\mathbf{z}}_s))$.

Finally, we assume there are **no post-treatment confounders** (Assumption B4). That is, there are no variables that are affected by the treatment and that affect both the mediator and the outcome. In our example, we assume there are no areas of the brain that affect the activation in the area of interest and that also affect areas involved in the conscious report of pain. This assumption may be violated in our

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

case, as we focus on one area of interest while other regions in the brain may be at work. This assumption may be relaxed if we consider post-treatment confounders as part of the mediator.

Given assumptions A1-A5 and B1-B4, we can focus on the identification of the within-subject natural indirect and direct effects, as well as the controlled effect of the mediator. To identify the natural effects, we require the identification of the counterfactual quantities $E_i [Y_{ij}(\bar{\mathbf{z}}_1, M(\bar{\mathbf{z}}_1))]$ and $E_i [Y_{ij}(\bar{\mathbf{z}}_1, M(\bar{\mathbf{z}}_0))]$. The first quantity can be readily identified using assumptions B1 and B3 as

$$E_i [Y_{ij} | \bar{\mathbf{Z}}_j = \bar{\mathbf{z}}_1] = E_i [Y_{ij}(\bar{\mathbf{z}}_1, M(\bar{\mathbf{z}}_1))].$$

As for the second one, we can identify its subject-level expectation across sub-trials using the above assumptions:

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

$$E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0))] = E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0)) \mid \bar{\mathbf{Z}}_s = \bar{\mathbf{z}}_1] \quad (4.1)$$

$$= E_{M_i(\bar{\mathbf{z}}_0)} \left[E_i [Y_{ij}(\bar{\mathbf{z}}_1, m) \mid \bar{\mathbf{Z}}_s = \bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0) = m] \right] \quad (4.2)$$

$$= \int E_i [Y_{ij}(\bar{\mathbf{z}}_1, m) \mid \bar{\mathbf{Z}}_j = \bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0) = m] dF_{M_{ij}(\bar{\mathbf{z}}_0)}(m) \quad (4.3)$$

$$= \int E_i [Y_{ij}(\bar{\mathbf{z}}_1, m) \mid \bar{\mathbf{Z}}_j = \bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_1) = m] dF_{M_{ij}(\bar{\mathbf{z}}_0)}(m) \quad (4.4)$$

$$= \int E_i [Y_{ij}^{obs} \mid \bar{\mathbf{Z}}_j = \bar{\mathbf{z}}_1, M_{ij}^{obs} = m] dF_{M_{ij}^{obs} \mid \mathbf{z}_j = \bar{\mathbf{z}}_0}(m). \quad (4.5)$$

In this derivation, line (4.1) follows from assumption B1, lines (4.2) and (4.3) follow from the law of iterated expectations, line (4.4) follows from assumption B2 and B4, and line (4.5) follows from assumption B3.

The identification of the within-subject controlled effect of the mediator requires a stronger version of assumption B2, which dictates that sequential ignorability holds over all levels that the mediator can take: For fixed level of treatment $\bar{\mathbf{z}}_s$, and for all levels of mediator m , the distribution of $Y_{ij}(\bar{\mathbf{z}}_s, m)$ is independent of $M_{ij}(\bar{\mathbf{z}}_{s'})$. Given the latter and assumptions B1-B4, we can identify the controlled effect of the mediator.

As a side note, we would like to note that if we assume the expectation $E_i [Y_{ij}^{obs} \mid \bar{\mathbf{Z}}_j = \bar{\mathbf{z}}_1, M_{ij}^{obs} = M]$ is linear, and the direct effect of the treatment does

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

not vary across levels of the mediator (there is no treatment-mediator interaction), then the natural indirect effect is equal to the controlled effect of the mediator, scaled by the changes the treatment had on the mediator:

$$E_i [Y_{ij}(\bar{\mathbf{z}}_1, M) - Y_{ij}(\bar{\mathbf{z}}_1, M')] E_i [M_{ij}(\bar{\mathbf{z}}_1) - M_{ij}(\bar{\mathbf{z}}_0)].$$

Finally, we define population-level expectation of the natural indirect effect as:

$$E \left[E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_1))] - E_i [Y_{ij}(\bar{\mathbf{z}}_1, M_{ij}(\bar{\mathbf{z}}_0))] \right], \quad (4.6)$$

where the outer expectation is with respect to the sampling of subjects, and the inner expectations are over the sampling of within-subject trials.

4.3.3 Estimation and inference

We now describe a method of estimation of the population level natural indirect effect in equation 4.6. The strategy is as follows.

1. We pose subject-level models for the expected value of the outcome given the treatment and mediator, $E_i [Y_{ij}^{obs} | \bar{\mathbf{Z}}_j, M_{ij}^{obs}]$. These models can be of any form, for example, they can be non-parametric if the mediator is binary, or fully parametric model when the mediator is continuous. Fitting separate models allows the direct and indirect effects to vary across participants. In order to have the

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

same flexibility when fitting one model for all participants, we rely on parametric forms and interaction terms for the effects of the treatment and mediator on the outcome with binary variables indicating subjects. This also can potentially introduce unobserved confounding across participants. An example of a model for the outcome given treatment and mediator will be presented in equation (4.8).

2. For each participant i , we use the model $E_i [Y_{ij}^{obs} | \bar{\mathbf{Z}}_j, M_{ij}^{obs}]$ and equation (4.5) to predict their average outcome under noxious heat and mediator values under non-noxious heat, using their own distribution of observed mediator values under non-noxious heat to make the prediction.
3. For each participant, we obtain the ws-NIE by taking the average outcome under noxious heat and subtract it from the predicted average outcome under noxious heat treatment and mediator levels under the non-noxious heat condition.
4. We proceed to take the sample average over all ws-NIE and obtain the population-level natural indirect effect.

We propose the use of the bootstrap to compute inferences about the population-level natural indirect effect. After calculating the subject-level natural indirect effects, we construct bootstrap samples by re-sampling from the pool of subject-level estimates. We repeat B times and construct 95% bootstrap intervals by taking the 2.5% and 97.5% percentiles of the bootstrap distribution of the parameters. This bootstrap

sampling scheme for hierarchical data is described by Davison and Hinkley.¹¹⁵

4.4 Application to Thermal Pain Experiment

We used functional causal mediation analysis¹⁴ to assess whether the right anterior insula mediates the effect of the noxious thermal stimuli on pain report, as introduced in section 4.2. Data that are collected densely in time from a continuous process can be denoted as ‘functional data’, and there are particular methods developed for their analysis (see Chapter 3). In this study, the fMRI BOLD signal represents a functional mediator, and it was recorded every two seconds for the duration of each trial. Every trial lasted 46 seconds in total.

We defined Z_{ij} to be the treatment received for participant i at trial j , $\{M_{ij}(t)\}_{t=1}^{46}$ as the average BOLD intensity for the Right Anterior Insula region in participant i at trial j , and Y_{ij} as the pain reported by participant i at trial j .

For each person i , we define the following scalar-function-scalar mediation model:

$$M_{ij}(t) = \delta_{1i}(t) + \alpha_i(t)Z_{ij} + \epsilon_{ij}(t) \quad (4.7)$$

$$Y_{ij} = \delta_{2i} + \gamma_i Z_{ij} + \int \beta_i(t)M_{ij}(t) dt + \eta_{ij}. \quad (4.8)$$

where $t \in [1, 46]$.

We begin by assuming all the necessary assumptions for the within-subject design

(assumptions A1-A5), and those required for causal mediation (assumptions B1-B4). If we assume that the models are correct - that the relation is linear, and there is no treatment-mediator interaction, then the natural direct and indirect effects for person i are γ_i and $\int \alpha_i(t)\beta_i(t) dt$, respectively. Meanwhile, the controlled effect of the mediator and the time decomposition of the indirect effect for person i are $\beta_i(t)$ and $\alpha_i(t)\beta_i(t)$, respectively. These are considered the within-subject parameters.

4.4.1 Within-subject estimation

For each person, we estimated the parameters using functional data analysis methods.⁴¹ For model (4.7) we used a two-step approach developed by Fan *et al.*⁹³ This approach estimates linear parameters at each time-point for the functional mediator, then penalizes the estimated coefficients via local polynomial smoothing. The bases set used for regularization consisted of 15 cubic b-splines,¹¹⁶ fitted with penalty on the second derivative to smooth the estimated coefficients. The smoothing parameters were chosen using Restricted Maximum Likelihood Estimation. For model (4.8), we used a functional generalized additive model.^{96,97} This regression model decomposes the functional parameter into splines and then penalizes them using random effects. For estimation of the functional parameter, we used 15 cubic P-splines⁹⁴ with second order penalty. We also chose the amount of penalization via generalized cross-validation.⁹⁵

Figure 4.1 depicts the estimated within-person functional parameters defined

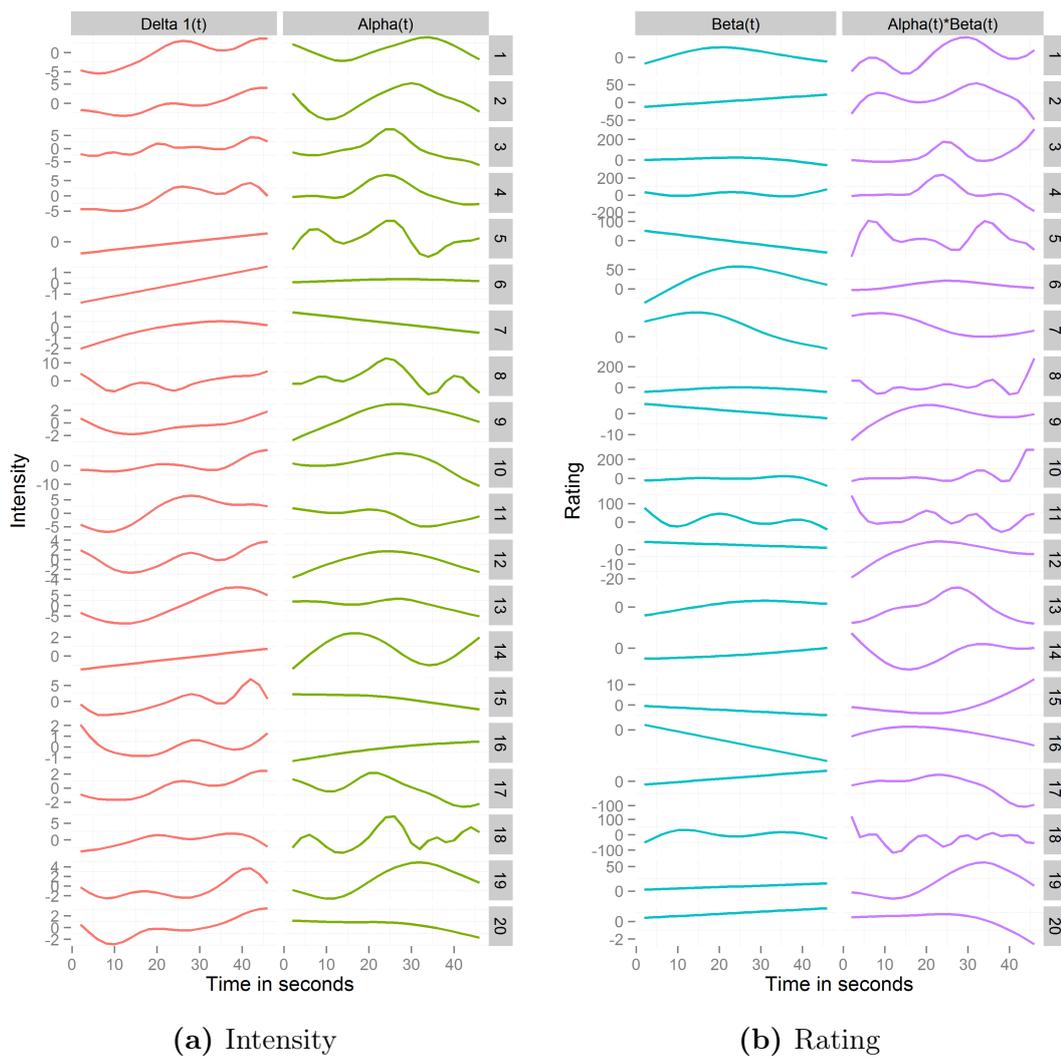


Figure 4.1: Within-subject estimates of functional coefficients for brain mediation of pain

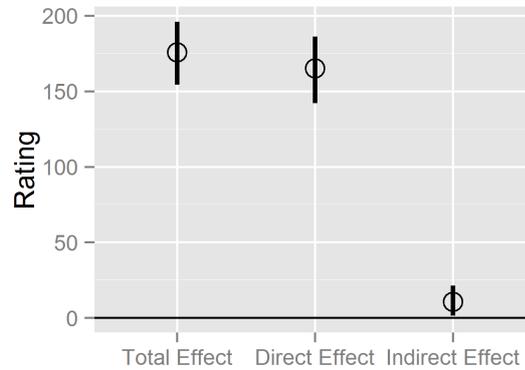
in models (4.7) and (4.8). The functional estimates pertaining the effect of the thermal stimuli (the treatment, Z_{ij}) on the average BOLD intensity (the mediator $\{M_{ij}(t)\}_{t=1}^{46}$), appear in Figure 4.1 (a). Meanwhile, the functional estimates for the controlled effect of the Right Anterior Insula, and the time decomposition of the indirect effect, are shown in Figure 4.1 (b). These estimates highlight the heterogeneity in response across participants, where some participants seem to have small or larger effects of the treatment on the mediator ($\text{Alpha}(t)$), and of the controlled effect of the mediator ($\text{Beta}(t)$).

4.4.2 Population-level estimation and inference

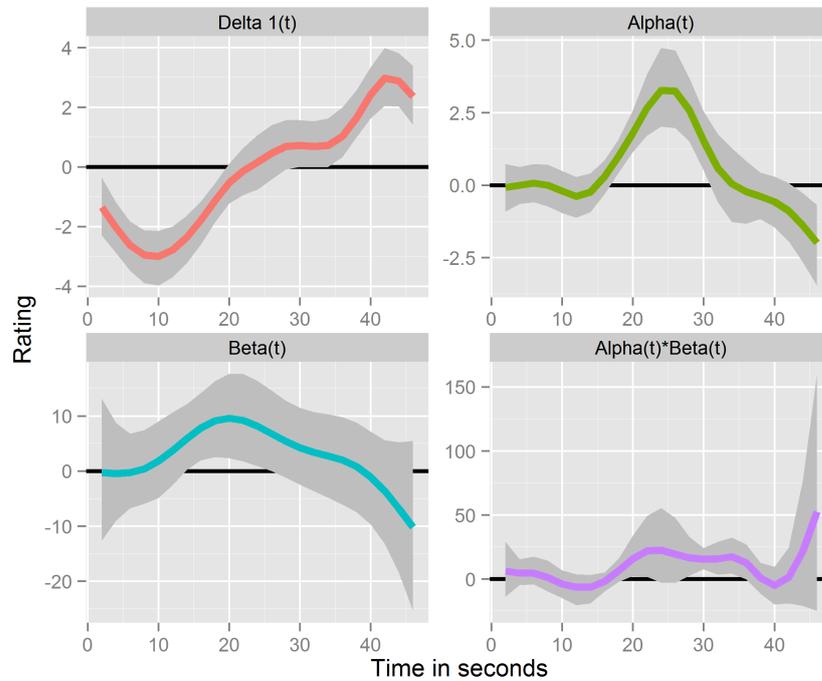
In order to get population-level estimates of causal mediation effects, we took the pointwise average of the estimated within-subject parameters. We computed pointwise 95% bootstrap intervals for making inferences. In this case, we bootstrapped the estimated within-subject parameters; that is, we sampled with replacement participant's identifiers, then we build our bootstrap samples incorporating the complete estimated functional parameter for the sampled participants. We then, at each time point, took the 2.5th and 97.5th percentiles of the bootstrap distribution to construct the 95% bootstrap interval. We define the 95% bootstrap band as the area covered by each of the bootstrap intervals, interpolating linearly between time points.

The estimates for the total effect, the natural direct and indirect effects, and the population level functional parameters, are shown in Figure 4.2, along with 95%

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION



(a) Total and natural effects



(b) Functional estimates

Figure 4.2: Across-subject estimates of functional coefficients, and causal mediation effects, with 95% Bootstrap pointwise Intervals. In (a), we show the average causal effect of noxious heat on pain rating (the total effect), as well as the estimates of the natural direct and indirect effects. In (b), $\Delta_1(t)$ represents the average BOLD response among trials under non-noxious heat, $\alpha(t)$ represents the average causal effect of noxious heat on the BOLD response, $\beta(t)$ is the controlled effect of the BOLD response on pain, and $\alpha(t)\beta(t)$ is the time decomposition of the natural indirect effect.

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

Bootstrap intervals and bands. Averaging across participants, applying noxious heat lead to pain ratings 176 points higher than non-noxious heat (95%BI 154-196). The variability for this estimate is reduced, as the levels of noxious heat were calibrated to elicit particular pain ratings.

Before addressing the natural direct and indirect effects, we investigate the functional parameters of interest. On average, the activation in the Right Anterior Insula under non-noxious heat ($\Delta 1(t)$), as measured by the BOLD contrast, has a low depression in the first 10 seconds, followed by a steady rise and a small decline. The average treatment effect on the activation in the right Anterior Insula has an abrupt increase at time 15, peaking at time 25 and decreasing onwards. The controlled effect of the activation in the Right Anterior Insula on pain rating ($\text{Beta}(t)$) shows more variability; it has a rise after 15 seconds, peaks at 25 seconds and declines steadily. The time decomposition of the natural indirect effect shows a positive contribution from 20 to 35 seconds, with less variability at the end of this interval.

As for causal mediation effects, the activation in the Right Anterior Insula has a small positive natural indirect effect (10.7, 95% BI 1.4-21.3), while the natural direct effect was much larger (186.2, 95% BI 142.1-165.3). Therefore, the effect of noxious heat, compared to non-noxious heat, on pain ratings is partly mediated by activation in the right anterior insula. The time decomposition of the natural indirect effect shows that activation during seconds 20 through 35 lead to an increase in pain ratings. These results rely on whether assumptions A1-A6 and B1-B4 hold.

4.5 Discussion

The within-subject design for mediation presents new opportunities for identification of causal mediation effects. This design trades assumptions about ignorability of the mediator assignment across participants to ignorability within participant. While unobserved confounding in the mediator-outcome relation can appear when we make comparison across participants, the within-subject design is potentially subject to confounding due to period and order effects - both observed variables. For now, we have assume we had control over carry-over effects, and that period does not have an influence on either the mediator or the outcome. Future work will be on relaxing these assumptions.

We exemplified the proposed method for estimation with the study of how a particular brain region - the right anterior insula - mediates the response to thermal pain. In this context, some assumptions needed for identification of the sub-trials and the identification of the causal mediation effects may be tenable, while others do not.

For example, we have made assumption A1 regarding our application of the method to the pain trial. This assumption, that there is no measurement error in the BOLD signal, is known not to hold. Therefore, we need methods that can account for measurement error, exploiting the multiple observation of mediators within subjects. We plan on expanding SIMEX¹¹⁷ to accommodate the added variance in M_{ij} , which can be modeled using observed measures of sources of bias.

Assumptions A2, temporal consistency, A3, control of carry-over effects, and as-

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

assumptions A4 and A6, no treatment by period interaction for the mediator nor for the outcome, may be testable up to some extent. Given that subjects participated in several runs, there are certain experimental designs that will allow for the identification of period and order effects. This will rely on the assumption of temporal consistency across runs. From another standpoint, one could use an experimental design that assigns different treatment regimes to different participants, and try to identify period-order effects by pooling information across participants. This will rely on making ignorability assumptions across subjects, making inferences subject to unobserved confounding again.

We also require that the within-subject design for fMRI studies have a particular structure, summarized in assumption A5 (the potential mediators and outcomes are related solely to one stimulus). This design is typically applied when studying mediation, and was applied in the pain trial that we studied.

For the identification of the causal mediation effects, assumption B1 (individual ignorability of the treatment assignment) is tenable given that the treatment regime was designed pseudo-randomly for each subject. Assumption B2 (individual sequential ignorability), as discussed previously, may be more tenable within a subject. In this case, we are not subject to confounding due to baseline characteristics, but we are to characteristics that change over time. Time since smoking could be of concern, as it is related to pain tolerance,¹¹³ but has been shown to not affect the subjective pain rating.¹¹⁴

CHAPTER 4. WITHIN-SUBJECT DESIGNS FOR MEDIATION

Whereas assumption B3, the consistency assumption, is guaranteed in designs of experiments,⁵ assumption B4 may be violated in the pain trial. Assumption B4 requires there are no post-treatment confounders. Since we are focused on one particular brain region, the right anterior insula, there may be many other regions that are modified by receiving a noxious heat touch and that also impact activation in the right anterior insula. Defining mediation effects in this particular setting is complex, and it may be that we need to define the activation in the whole brain as the mediator. Functional data methods that can handle smoothing over space and time for large data will allow us to assess whole-brain mediation.

Finally, we made assumptions about linearity and no treatment-mediator interaction to facilitate the use of functional mediation models. More work is needed to extend the latter to incorporate possible interactions as well as other observed confounders.

On another note, one drawback of making inferences within a subject is the large reduction in sample size. In our application, even when we have over 40 observations per subject, a complex functional parameter is better estimated with more observations. More work is needed to support hierarchical models that can adjust for confounding across and within-subjects using parametric and semi-parametric theory, and to assess the trade-off of increasing the number of trials or the number of participants.

Chapter 5

Conclusion

In the present work, I have contributed to the causal inference literature in areas like measurement error and mediation and functional data analysis. In addition, two of these methods add to the analysis of neuroimaging data, and the third can potentially contribute to the field as well. All methods presented are among the first steps in their field, and can have many extensions.

More specifically, in chapter 2, I proposed a solution to the use of mismeasured variables in the design of observational studies that aim at estimating the causal effect of a treatment using propensity score methods, like estimating the effects that living in a disadvantaged neighborhood in adolescent drug use. This solution, multiple imputation for external calibration, relies on the assumption that the joint distribution of treatment, outcome, and confounding variables is multivariate normal. Nevertheless, the method remains robust to some level of misspecification, as it performs very

CHAPTER 5. CONCLUSION

well even though the treatment in consideration is binary, and when the outcome's distribution is far from a normal distribution. It is also robust to the varying sizes of the main study sample, but correcting for large amounts of measurement error requires larger calibration samples. The method is applicable to the estimation of both the average treatment effect and the average treatment effect on the treated.

A natural extension of this topic would be to use another method of imputation that does not depend on the joint-normality assumption, such as multiple imputation using chained equations.¹¹⁸ Additionally, I would like to assess the performance of the method under other propensity score methods beyond inverse probability of treatment weighting, like propensity score matching.

In Chapter 3, I extended the functional mediation framework introduced by Lindquist (2012) to settings where a scalar treatment influences a scalar mediator and a functional outcome, as well as to settings where the scalar treatment impacts a functional mediator and a functional outcome. We can use this framework to investigate the pain experience, as well as how different regions of the brain communicate in response to pain. I derived direct and indirect effects that map to causal mediation effects under certain assumptions detailed in the appendix. Finally, I developed R algorithms to estimate functional mediation effects, and used them to estimate functional mediation in two pain studies.

One extension of the work in Chapter 3 is to define mediation effects for functional treatments, for scalar and functional mediators and outcomes, and develop methods

CHAPTER 5. CONCLUSION

for their estimation. Another extension is to add more functionality to the R functions that I developed. The incorporation of confounding variables and building an R package are next steps.

Lastly, in Chapter 4, I developed a framework to assess causal mediation under an experimental design - the within-subject design - that has not been considered much in the causal inference literature. This design is common in neuroscience experiments, and we use it to investigate the pain induced by noxious thermal stimuli. In this design, subjects receive multiple treatments at multiple times. Given this design, I formulated assumptions to identify sub-trials within an experimental regime, and to identify causal mediation effects. I also proposed a method of estimation, and applied it to a trial to study thermal pain.

The latter work is the first step in the study of within-subject designs for causal mediation. In this work, some of the assumptions that I proposed for the identification of sub-trials can be very strong. More work is needed for developing methods to test for violations of these assumptions, and to incorporate observed within-subject confounders, like period effects. Finally, the within-subject design has a structure that can be very helpful to address measurement error in the mediator or outcome variables. An extension like this would be very helpful for studies that use fMRI data.

This dissertation presents three different topics in causal inference: propensity score methods and measurement error, functional mediation, and a particular design of experiments for mediation. These seemingly unrelated topics share underlying

CHAPTER 5. CONCLUSION

scientific goals. The first is that of measurement error and causal inference. My work in Chapter 2 focuses directly on a solution to the measurement error problem in propensity score analysis, while my work in Chapter 4 provides the groundwork for addressing measurement error in fMRI data as mediators. The second goal is the development of causal mediation methods for neuroimaging studies. Chapters 3 and 4 present new methods for assessing mediation in neuroscience experiments using fMRI. Chapter 3 has provided a new method to investigate functional connectivity, which is the way to areas of the brain communicate in response to a stimulus. Meanwhile, Chapter 4 has developed causal mediation methods for a design that is commonly used in neuroimaging studies. Instead of using the identifying assumptions applicable to randomized controlled trials, researchers can and should consider the assumptions presented in Chapter 4.

Beyond the latter scientific goals, and the advancement of statistical methodology, remains a hope. A hope that the methods hereby developed can help and are used to address public health problems. There are many examples of measurement error in variables of public health interest, such as reported variables like weight or diet, and among constructs like depression, anxiety, and self-efficacy. Whenever those variables are used in a propensity score models, a method that takes such measurement error into account is needed to ensure causal comparisons. Also, public health interventions can be better understood with mediation. Functional mediation can help researchers use all the information that is available in variables that are collected densely in time

CHAPTER 5. CONCLUSION

or space, such as how active is a person, their exposure to pollutants in the past year, or their history of medication, instead of restricting themselves to using one summary variable. Moreover, addressing the true design of experiments used in neuroscience allows us to see its advantages and disadvantages in making causal statements, and sets an example for other interventions in public health. Finally, causal mediation methods for fMRI data will permit the understanding of how changes in the brain can mediate the effect of interventions on health outcomes. May this work aid in the better of public health.

Chapter 6

Appendix

6.1 Appendix for Chapter 2: Simulation details and code

The the online companion to Chapter 2 is available at

http://ywebbvar.github.io/PS_MIEC/.

You can see the details of the simulations, color figures and code by following the links:

Normal scenario:

- Normal ‘Y’, normal (X,Z,W)
- Normal ‘Y’, normal (X,Z,W), including a simple imputation method
- Normal ‘Y’, normal (X,Z,W), with varying sample sizes for calibration and main

CHAPTER 6. APPENDIX

data sets

- Normal ‘Y’, normal (X,Z,W), estimating Average Treatment effect on the Treated (ATT)

Non-normal scenarios:

- Normal ‘Y’, mixture (X,Z,W)
- Bernoulli ‘Y’, normal (X,Z,W)
- Bernoulli ‘Y’, mixture (X,Z,W)
- Mixture ‘Y’, normal (X,Z,W)
- Mixture ‘Y’, mixture (X,Z,W)
- Normal ‘Y’, normal (X,Z,W), where Z is a binary variable

You can see the code for Guo, Little and McConnell’s Multiple Imputation for External Calibration, or download the R script we used in the simulations.

6.2 Appendix for Chapter 3: Assumptions for causal identification of mediated effects

Assumptions are required to interpret the parameters as causal mediation effects. Lindquist¹⁴ defined assumptions for the identification of causal mediated effects for

the scalar-function-scalar mediation model. I present assumptions that suffice for the identification of causal mediated effects for the scalar-scalar-function and the scalar-function-function mediation models.

6.2.1 Scalar-Scalar-Function model

Let's begin by reformulating the scalar-scalar-function mediation model (found in equations (3.7) and (3.8)) in terms of potential mediators and potential outcomes. Let X_i be the treatment that participant i receives, $M_i(x)$ be the potential mediator that participant i has under treatment x , and let $\{Y_{it}(x, m)\}_{t=0}^1$ be the time series of potential outcomes for participant i under treatment x and mediator level m . Note the change in notation, as time is now indexed as a subscript and treatment is now marked between parenthesis.

We define causal models analogous to those in equations (3.7) and (3.8):

$$M_i(x) = \delta_1 + \alpha x + \epsilon_i, \quad (6.1)$$

$$Y_{it}(x, m) = \delta_{2t} + \gamma_t x + \beta_t m + \eta_{it}. \quad (6.2)$$

where $t \in [0, 1]$.

The first assumption is that the previous models are correct. We assume the response is linear, and that, given the functional effects of the treatment and the mediator, the η_{it} errors are independent across time points t and across participants

CHAPTER 6. APPENDIX

i. For the moment, we do not include interaction terms for the effect of the treatment and the mediator on the outcome, but this assumption can be relaxed.

The second assumption is ignorability of treatment assignment. This assumption states that the assignment of the treatment is not influenced by any variables that are related to the outcome or the mediator. Formally, it is defined as:

$$M_i(0), M_i(1), \{Y_{it}(0), Y_{it}(1)\}_{t \in [0,1]} \perp\!\!\!\perp X_i$$

for all participants *i*.

The third assumption is the ignorability of the mediator assignment. In this assumption, we require that there are no confounders of the mediator relation with each time point of the outcome. In particular, we only need to have the potential outcomes be independent of the potential mediators under the opposite treatment condition. That is:

$$\{Y_{it}(x, m)\} \perp\!\!\!\perp M(1 - x) \mid X = x,$$

for all time points *t*, all participants *i*, all treatments *x*, and all mediator levels *m*. This assumption can be relaxed to hold under levels of baseline confounders, but not for confounders that are themselves affected by the treatments (post-treatment confounders).

The proof of identification of the potential outcome $Y_{it}(1, M_i(0))$ is as follows:

$$E [Y_{it}(1, M_i(0))] = E [Y_{it}(1, M_i(0)) | X_i = 1] \quad (6.3)$$

$$= E_{M_i(0)} \left[E_i [Y_{it}(1, m) | X_i = 1, M_i(0) = m] \right] \quad (6.4)$$

$$= \int E_i [Y_{it}(1, m) | X_i = 1, M_i(0) = m] dF_{M_i(0)}(m) \quad (6.5)$$

$$= \int E_i [Y_{it}(1, m) | X_i = 1, M_i(1) = m] dF_{M_i(0)}(m) \quad (6.6)$$

$$= \int E_i [Y_{it}^{obs} | X_i = 1, M_i^{obs} = m] dF_{M_i^{obs} | \mathbf{Z}_j=0}(m). \quad (6.7)$$

In this derivation, line (6.3) follows from ignorability of the treatment, lines (6.4) and (6.5) follow from the law of iterated expectations, line (6.6) follows from ignorability of the mediator, and line (6.7) follows from no post-treatment confounders.

6.2.2 Scalar-Function-Function model

We now reformulate the scalar-function-function mediation model (found in equations (3.10) and (3.11)) in potential outcomes notation. The treatment that participant i receives remains denoted by X_i , the time series $M_{it}(x) = \{M_{is}(x)\}_{s \in [0, t]}$ is the history of the potential mediator that participant i has under treatment x up to time t , and the time series $\{Y_{it}(x, m)\}_{t=0}^1$ is the potential outcome for participant i under treatment x and mediator level m .

We define causal models for the models in equations (3.10) and (3.11):

CHAPTER 6. APPENDIX

$$M_{is}(x) = \delta_{1s} + \alpha_s x + \epsilon_{is}, \quad (6.8)$$

$$Y_{it}(x, m) = \delta_{2t} + \gamma_t x + \int_0^t \beta_{\{s,t\}} m_t ds + \eta_{it}. \quad (6.9)$$

where $t \in [0, 1]$.

We require that the previous models are correct, assuming the response is linear at each time point of M_{it} and Y_{it} , and that, given the functional effects of the treatment and the mediator, the η_{it} and ϵ_{is} errors are each independent across time points t and across participants i . Also, we do not include interaction terms for the effect of the treatment and the mediator on the outcome, but this assumption can be relaxed.

We also require ignorability of treatment assignment. In this context, it requires:

$$\{M_{is}(0), M_{is}(1)\}_{s \in [0,1]}, \{Y_{it}(0), Y_{it}(1)\}_{t \in [0,1]} \perp\!\!\!\perp X_i$$

for all participants i .

We further assume ignorability of the mediator assignment. This assumption is required to be much stronger, as we require it to hold for all time points of the outcome and all time points in the history of the mediator. That is:

$$\{Y_{it}(x, m)\} \perp\!\!\!\perp \{M_{is}(1 - x)\}_{s \in [0,t]} \mid X = x,$$

CHAPTER 6. APPENDIX

for all time points t , all participants i , all treatments x , all mediator levels m . This assumption can also be relaxed to hold under levels of baseline confounders, but not for post-treatment confounders.

The proof of identification of the potential outcome $Y_{it}(1, \{M_{is}(0)\}_{s \in [0,t]})$ is as follows:

$$E [Y_{it}(1, \{M_{is}(0)\}_{s \in [0,t]})] = E [Y_{it}(1, \{M_{is}(0)\}_{s \in [0,t]}) \mid X_i = 1] \quad (6.10)$$

$$= E_{M_{it}(0)} \left[E_i [Y_{it}(1, m) \mid X_i = 1, \{M_{is}(0)\}_{s \in [0,t]} = m] \right] \quad (6.11)$$

$$= \int E_i [Y_{it}(1, m) \mid X_i = 1, \{M_{is}(0)\}_{s \in [0,t]} = m] dF_{M_{it}(0)}(m) \quad (6.12)$$

$$= \int E_i [Y_{it}(1, m) \mid X_i = 1, \{M_{is}(1)\}_{s \in [0,t]} = m] dF_{M_{it}(0)}(m) \quad (6.13)$$

$$= \int E_i [Y_{it}^{obs} \mid X_i = 1, M_{is}^{obs} = m] dF_{M_{it}^{obs} \mid \mathbf{Z}_j=0}(m). \quad (6.14)$$

Similarly to the previous section, line (6.10) follows from ignorability of the treatment, lines (6.11) and (6.12) follow from the law of iterated expectations, line (6.13) follows from ignorability of the mediator, and line (6.14) follows from no post-treatment confounders.

6.3 Appendix for Chapter 3: Simulation details and code

The the online companion to Chapter 3 is available at:

http://ywebbvar.github.io/functional_mediation/.

You can see the details of the simulations, color figures and code by following the links:

- Scalar-function-scalar mediation simulations and its code to run the model
- Scalar-scalar-function mediation and its code to run the model
- Scalar-function-function mediation and its code to run the model

Bibliography

- [1] J. S. Neyman, D. Dabrowska, and T. Speed, “On the Application of Probability Theory to Agricultural Experiments. Essay on Principles. Section 9.” *Statistical Science*, vol. 5, no. 4, pp. 465–472, 1990.
- [2] D. B. Rubin, “Estimating causal effects of treatments in randomized and non-randomized studies.” *Journal of Educational Psychology*, vol. 66, no. 5, pp. 688–701, 1974.
- [3] D. Rubin, “Inference and missing data,” *Biometrika*, vol. 63, no. 3, pp. 581–592, 1976.
- [4] K. E. Rudolph, E. A. Stuart, T. A. Glass, and K. R. Merikangas, “Neighborhood disadvantage in context: the influence of urbanicity on the association between neighborhood disadvantage and adolescent emotional disorders,” *Social Psychiatry and Psychiatric Epidemiology*, vol. 49, no. 3, pp. 467—475, 2014.
- [5] S. R. Cole and C. E. Frangakis, “The consistency statement in causal inference: a definition or an assumption?” *Epidemiology*, vol. 20, no. 1, pp. 3–5, Jan. 2009.

BIBLIOGRAPHY

- [6] D. B. Rubin, “Randomization Analysis of Experimental Data: The Fisher Randomization Test Comment,” *Journal of the American Statistical Association*, vol. 75, no. 371, pp. 591–593, 1980.
- [7] —, “Comment: Neyman (1923) and Causal Inference in Experiments and Observational Studies,” *Statistical Science*, vol. 5, no. 4, pp. 472–480, 1990.
- [8] P. R. Rosenbaum and D. B. Rubin, “The central role of the propensity score in observational studies for causal effects,” *Biometrika*, vol. 70, no. 1, pp. 41–55, 1983.
- [9] E. A. Stuart, “Matching methods for causal inference: A review and a look forward.” *Stat. Sci.*, vol. 25, no. 1, pp. 1–21, Feb. 2010.
- [10] E. P. Martens, W. R. Pestman, A. de Boer, S. V. Belitser, and O. H. Klungel, “Systematic differences in treatment effect estimates between propensity score methods and logistic regression.” *Int. J. Epidemiol.*, vol. 37, no. 5, pp. 1142–7, Oct. 2008.
- [11] C. M. Judd and D. a. Kenny, “Process Analysis: Estimating Mediation in Treatment Evaluations,” *Evaluation Review*, vol. 5, no. 5, pp. 602–619, Oct. 1981.
- [12] R. M. Baron and D. a. Kenny, “The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considera-

BIBLIOGRAPHY

- tions.” *Journal of Personality and Social Psychology*, vol. 51, no. 6, pp. 1173–82, Dec. 1986.
- [13] T. J. Vanderweele, “Invited commentary: structural equation models and epidemiologic analysis.” *American Journal of Epidemiology*, vol. 176, no. 7, pp. 608–12, Oct. 2012.
- [14] M. A. Lindquist, “Functional Causal Mediation Analysis With an Application to Brain Connectivity,” *Journal of the American Statistical Association*, vol. 107, no. 500, pp. 1297–1309, Dec. 2012.
- [15] M. E. Sobel, “Asymptotic confidence intervals for indirect effects in structural equation models,” *Sociological methodology*, vol. 13, no. 1982, pp. 290–312, 1982. [Online]. Available: <http://ripl.faculty.asu.edu/wp-content/uploads/2013/02/Sobel-1982.pdf>
- [16] D. P. MacKinnon, C. M. Lockwood, J. M. Hoffman, S. G. West, and V. Sheets, “A comparison of methods to test mediation and other intervening variable effects.” *Psychological Methods*, vol. 7, no. 1, pp. 83–104, 2002.
- [17] S. Wright, “Correlation and causation,” *Journal of Agricultural Research*, vol. 20, no. 7, pp. 557–585, 1921.
- [18] K. A. Bollen, *Structural Equations with Latent Variables*. John Wiley and Sons, Inc., 1989.

BIBLIOGRAPHY

- [19] B. Jo, “Causal inference in randomized experiments with mediational processes.” *Psychological methods*, vol. 13, no. 4, pp. 314–36, Dec. 2008.
- [20] M. Hallett, “Transcranial magnetic stimulation and the human brain.” *Nature*, vol. 406, no. 6792, pp. 147–50, Jul. 2000.
- [21] J. Pearl, “Direct and Indirect Effects,” in *UAI’01 Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*, no. 1992. San Francisco, CA, USA: Morgan Kaufmann Publishers Inc., 2001, pp. 411–420.
- [22] B. Egleston, D. O. Scharfstein, B. Munoz, and S. West, “Investigating mediation when counterfactuals are not metaphysical: Does sunlight UVB exposure mediate the effect of eyeglasses on cataracts?” 2006.
- [23] J. M. Robins and S. Greenland, “Identifiability and exchangeability for direct and indirect effects,” *Epidemiology*, vol. 3, no. 2, pp. 143–155, 1992.
- [24] C. E. Frangakis and D. B. Rubin, “Principal stratification in causal inference.” *Biometrics*, vol. 58, no. 1, pp. 21–9, Mar. 2002.
- [25] R. Gallop, D. S. Small, J. Y. Lin, M. R. Elliott, M. M. Joffe, and T. R. T. Have, “Mediation analysis with principal stratification,” *Statistics in Medicine*, vol. 28, pp. 1108–1130, 2009.
- [26] B. Jo, E. a. Stuart, D. P. MacKinnon, and A. D. Vinokur, “The Use of Propen-

BIBLIOGRAPHY

- sity Scores in Mediation Analysis.” *Multivariate Behavioral Research*, vol. 46, no. 3, pp. 425–452, May 2011.
- [27] K. Imai, L. Keele, and T. Yamamoto, “Identification, Inference and Sensitivity Analysis for Causal Mediation Effects,” *Statistical Science*, vol. 25, no. 1, pp. 51–71, Feb. 2010.
- [28] T. R. Ten Have and M. M. Joffe, “A review of causal estimation of effects in mediation analyses.” *Statistical Methods in Medical Research*, vol. 21, no. 1, pp. 77–107, Feb. 2012.
- [29] J. S. Kaufman, R. F. Maclehorse, and S. Kaufman, “A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation.” *Epidemiologic perspectives & innovations : EP+I*, vol. 1, no. 1, p. 4, Jan. 2004.
- [30] T. J. VanderWeele, “Marginal structural models for the estimation of direct and indirect effects.” *Epidemiology*, vol. 20, no. 1, pp. 18–26, Jan. 2009.
- [31] C. E. Frangakis and D. B. Rubin, “Principal stratification in causal inference.” *Biometrics*, vol. 58, no. 1, pp. 21–9, Mar. 2002.
- [32] K. Imai, D. Tingley, and T. Yamamoto, “Experimental designs for identifying causal mechanisms,” *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, vol. 176, no. Part 1, pp. 5–51, 2013.
- [33] H. Jin and D. B. Rubin, “Principal Stratification for Causal Inference With

BIBLIOGRAPHY

- Extended Partial Compliance,” *Journal of the American Statistical Association*, vol. 103, no. 481, pp. 101–111, Mar. 2008.
- [34] —, “Public Schools Versus Private Schools: Causal Inference With Partial Compliance,” *Journal of Educational and Behavioral Statistics*, vol. 34, no. 1, pp. 24–45, Mar. 2009.
- [35] R. J. Carroll, D. Rupert, L. A. Stefanski, and C. M. Crainiceanu, *Measurement Error in Nonlinear Models*, May 2006, vol. 39, no. 2.
- [36] J. P. Buonaccorsi, *Measurement error. Models, Methods, and Applications*. Taylor and Francis Group, LLC, 2010.
- [37] W. A. Fuller, *Measurement Error Models*. John Wiley and Sons, Inc., 1987.
- [38] N. L. Strominger, R. J. Demarest, and L. B. Laemle, “Neurons and Associated Cells,” in *Noback’s Human Nervous System*. Totowa, NJ: Humana Press, 2012, ch. 2, pp. 11–38.
- [39] S.-g. Kim and P. A. Bandettini, “Principles of Functional MRI,” in *Functional MRI: Basic Principles and Clinical Applications*, S. H. Faro and F. B. Mohamed, Eds. New York, NY: Springer Science+Business Media, Inc, 2006, ch. 1, pp. 3–23.
- [40] R. A. Poldrack, J. A. Mumford, and T. E. Nichols, *Handbook of functional MRI data analysis*. Cambridge University Press, 2011.

BIBLIOGRAPHY

- [41] J. Ramsay and B. Silverman, *Functional Data Analysis*, 2nd ed. Springer Science+Business Media, Inc, 2005.
- [42] C. M. Crainiceanu, A.-M. Staicu, and C.-Z. Di, “Generalized Multilevel Functional Regression.” *Journal of the American Statistical Association*, vol. 104, no. 488, pp. 1550–1561, Dec. 2009.
- [43] X. Tan, M. P. Shiyko, R. Li, Y. Li, and L. Dierker, “A time-varying effect model for intensive longitudinal data.” *Psychological methods*, vol. 17, no. 1, pp. 61–77, Mar. 2012.
- [44] N. Malfait and J. O. Ramsay, “The historical functional linear model,” *Canadian Journal of Statistics*, vol. 31, no. 2, pp. 115–128, 2003.
- [45] P. T. Reiss and R. T. Ogden, “Functional Principal Component Regression and Functional Partial Least Squares,” *Journal of the American Statistical Association*, vol. 102, no. 479, pp. 984–996, Sep. 2007.
- [46] ———, “Functional generalized linear models with images as predictors.” *Biometrics*, vol. 66, no. 1, pp. 61–9, Mar. 2010.
- [47] I. M. Johnstone and A. Y. Lu, “On Consistency and Sparsity for Principal Components Analysis in High Dimensions.” *Journal of the American Statistical Association*, vol. 104, no. 486, pp. 682–693, Jun. 2009.

BIBLIOGRAPHY

- [48] S. Zhao, “Covariate Measurement Error Correction Methods in Mediation Analysis with Failure Time Data,” Ph.D. dissertation, University of Washington, 2012.
- [49] J. Goldsmith, J. Bobb, C. M. Crainiceanu, B. Caffo, and D. Reich, “Penalized Functional Regression.” *Journal of computational and graphical statistics : a joint publication of American Statistical Association, Institute of Mathematical Statistics, Interface Foundation of North America*, vol. 20, no. 4, pp. 830–851, Dec. 2011.
- [50] J. Gertheiss, J. Goldsmith, C. Crainiceanu, and S. Greven, “Longitudinal scalar-on-functions regression with application to tractography data.” *Biostatistics (Oxford, England)*, vol. 14, no. 3, pp. 447–61, Jul. 2013.
- [51] P. M. Steiner, T. D. Cook, and W. R. Shadish, “On the Importance of Reliable Covariate Measurement in Selection Bias Adjustments Using Propensity Scores,” *J. Educ. Behav. Stat.*, vol. 36, no. 2, pp. 213–236, Feb. 2011.
- [52] D. L. Millimet, “The Elephant in the Corner: A Cautionary Tale about Measurement Error in Treatment Effects Models,” in *Missing Data Methods Cross-sectional Methods Appl. Adv. Econom. Vol. 27A*, ser. Advances in Econometrics, D. M. Drukker, Ed. Bingley: Emerald Group Publishing, 2011, vol. 27, ch. Chapter 1, pp. 1–39.
- [53] D. F. McCaffrey, J. R. Lockwood, and C. M. Setodji, “Inverse probability

BIBLIOGRAPHY

- weighting with error-prone covariates,” *Biometrika*, vol. 100, no. 3, pp. 671–680, Jun. 2013.
- [54] B. Rosner, D. Spiegelman, and W. C. Willett, “Correction of logistic regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error.” *Am. J. Epidemiol.*, vol. 132, no. 4, pp. 734–45, Oct. 1990.
- [55] J. Cook and L. Stefanski, “Simulation-extrapolation estimation in parametric measurement error models,” *Journal of the American Statistical Association*, vol. 89, no. 428, pp. 1314–1328, 1994.
- [56] S. R. Cole, H. Chu, and S. Greenland, “Multiple-imputation for measurement-error correction.” *Int. J. Epidemiol.*, vol. 35, no. 4, pp. 1074–81, Aug. 2006.
- [57] Y. Guo, R. J. Little, and D. S. McConnell, “On using summary statistics from an external calibration sample to correct for covariate measurement error.” *Epidemiology*, vol. 23, no. 1, pp. 165–74, Jan. 2012.
- [58] T. Stürmer, S. Schneeweiss, J. Avorn, and R. J. Glynn, “Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration.” *Am. J. Epidemiol.*, vol. 162, no. 3, pp. 279–89, Aug. 2005.
- [59] A. Rotnitzky, J. M. Robins, and D. O. Scharfstein, “Semiparametric regression

BIBLIOGRAPHY

- for repeated outcomes with nonignorable nonresponse,” *J. Am. Stat. Assoc.*, vol. 93, no. 444, pp. 1321–1339, 1998.
- [60] D. B. Rubin, “Randomization Analysis of Experimental Data: The Fisher Randomization Test Comment,” *J. Am. Stat. Assoc.*, vol. 75, no. 371, pp. 591–593, Sep. 1980.
- [61] B. K. Lee, J. Lessler, and E. A. Stuart, “Improving propensity score weighting using machine learning.” *Stat. Med.*, vol. 29, no. 3, pp. 337–46, Feb. 2010.
- [62] X.-l. Meng, “Inferences with Uncongenial Sources of Input,” *Stat. Sci.*, vol. 9, no. 4, pp. 538–558, 1994.
- [63] J. L. Schafer, “Multiple Imputation in Multivariate Problems When the Imputation and Analysis Models Differ,” *Stat. Neerl.*, vol. 57, no. 1, pp. 19–35, Feb. 2003.
- [64] X. Liao, D. Spiegelman, and R. J. Carroll, “Regression calibration is valid when properly applied.” *Epidemiology*, vol. 24, no. 3, pp. 466–7, May 2013.
- [65] D. B. Rubin, *Multiple Imputation for Nonresponse in Surveys*. New York, NY: J. Wiley & Sons, 1987.
- [66] J. P. Reiter, “Multiple imputation when records used for imputation are not used or disseminated for analysis,” *Biometrika*, vol. 95, no. 4, pp. 933–946, Nov. 2008.

BIBLIOGRAPHY

- [67] S. C. Goslee and D. L. Urban, “The ecodist package for dissimilarity-based analysis of ecological data,” *Journal of Statistical Software*, vol. 22, no. 7, 2007.
- [68] R. C. Kessler, S. Avenevoli, E. J. Costello, J. G. Green, M. J. Gruber, S. Heeringa, K. R. Merikangas, B.-E. Pennell, N. A. Sampson, and A. M. Zaslavsky, “Design and field procedures in the us national comorbidity survey replication adolescent supplement (ncs-a),” *International Journal of Methods in Psychiatric Research*, vol. 18, no. 2, pp. 69–83, 2009.
- [69] —, “National comorbidity survey replication adolescent supplement (NCS-A): II. overview and design,” *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 48, no. 4, pp. 380–385, 2009.
- [70] K. R. Merikangas, J.-P. He, M. Burstein, S. A. Swanson, S. Avenevoli, L. Cui, C. Benjet, K. Georgiades, and J. Swendsen, “Lifetime prevalence of mental disorders in us adolescents: results from the national comorbidity survey replication–adolescent supplement (ncs-a),” *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 49, no. 10, pp. 980–989, 2010.
- [71] A. V. Diez Roux, C. I. Kiefe, D. R. Jacobs Jr, M. Haan, S. A. Jackson, F. J. Nieto, C. C. Paton, and R. Schulz, “Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies,” *Annals of Epidemiology*, vol. 11, no. 6, pp. 395–405, 2001.
- [72] A. V. D. Roux, L. N. Borrell, M. Haan, S. A. Jackson, and R. Schultz, “Neigh-

BIBLIOGRAPHY

- bourhood environments and mortality in an elderly cohort: results from the cardiovascular health study,” *Journal of Epidemiology and Community Health*, vol. 58, no. 11, pp. 917–923, 2004.
- [73] R. C. Kessler, S. Avenevoli, J. Green, M. J. Gruber, M. Guyer, Y. He, R. Jin, J. Kaufman, N. A. Sampson, A. M. Zaslavsky *et al.*, “National comorbidity survey replication adolescent supplement (ncs-a): Iii. concordance of dsm-iv/cidi diagnoses with clinical reassessments,” *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 48, no. 4, pp. 386–399, 2009.
- [74] E. H. Dugoff, M. Schuler, and E. A. Stuart, “Generalizing observational study results: applying propensity score methods to complex surveys.” *Health Services Research*, vol. 49, no. 1, pp. 284–303, Feb. 2014.
- [75] M. Cefalu and F. Dominici, “Does exposure prediction bias health-effect estimation?: the relationship between confounding adjustment and exposure prediction.” *Epidemiology*, vol. 25, no. 4, pp. 583–90, Jul. 2014.
- [76] D. B. Rubin, “The design versus the analysis of observational studies for causal effects : Parallels with the design of randomized trials,” *Statistics in Medicine*, vol. 26, pp. 20–36, 2007.
- [77] P. Arnstein, M. Caudill, C. L. Mandle, A. Norris, and R. Beasley, “Self efficacy as a mediator of the relationship between pain intensity, disability and depression in chronic pain patients,” *Pain*, vol. 80, no. 3, pp. 483–491, 1999.

BIBLIOGRAPHY

- [78] E. Sherman, A. Mathur, and R. B. Smith, “Store Environment and Consumer Purchase Behavior: Mediating Role of Consumer Emotions,” *Psychology & Marketing*, vol. 14, no. July 1997, pp. 361 – 378, 1997.
- [79] R. C. Liden, S. J. Wayne, and R. T. Sparrowe, “An examination of the mediating role of psychological empowerment on the relations between the job, interpersonal relationships, and work outcomes.” *The Journal of applied psychology*, vol. 85, no. 3, pp. 407–416, 2000.
- [80] L. Y. Atlas, R. a. Whittington, M. a. Lindquist, J. Wielgosz, N. Sonty, and T. D. Wager, “Dissociable influences of opiates and expectations on pain.” *The Journal of neuroscience : the official journal of the Society for Neuroscience*, vol. 32, no. 23, pp. 8053–64, Jun. 2012.
- [81] B. Huang, S. Sivaganesan, P. Succop, and E. Goodman, “Statistical assessment of mediational effects for logistic mediational models.” *Statistics in Medicine*, vol. 23, no. 17, pp. 2713–28, Sep. 2004.
- [82] D. P. MacKinnon, *Introduction to Statistical Mediation Analysis*. New York, NY: Taylor and Francis Group, LLC, 2008.
- [83] K. J. Preacher and A. F. Hayes, “Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models,” *Behavior Research Methods*, vol. 40, no. 3, pp. 879–891, Aug. 2008.

BIBLIOGRAPHY

- [84] T. VanderWeele and S. Vansteelandt, “Mediation Analysis with Multiple Mediators,” *Epidemiologic Methods*, vol. 2, no. 1, pp. 95–115, Jan. 2014.
- [85] S. Shiffman, A. a. Stone, and M. R. Hufford, “Ecological Momentary Assessment,” *Annual Review of Clinical Psychology*, vol. 4, no. 1, pp. 1–32, Apr. 2008.
- [86] A. Steptoe, E. Leigh Gibson, M. Hamer, and J. Wardle, “Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire,” *Psychoneuroendocrinology*, vol. 32, no. 1, pp. 56–64, 2007.
- [87] L. Xiao, L. Huang, J. a. Schrack, L. Ferrucci, V. Zipunnikov, and C. M. Crainiceanu, “Quantifying the lifetime circadian rhythm of physical activity: a covariate-dependent functional approach,” *Biostatistics*, vol. 16, no. 2, pp. 352–367, 2014.
- [88] D. Hedeker, R. J. Mermelstein, M. L. Berbaum, and R. T. Campbell, “Modeling mood variation associated with smoking: An application of a heterogeneous mixed-effects model for analysis of ecological momentary assessment (EMA) data,” *Addiction*, vol. 104, no. 2, pp. 297–307, 2009.
- [89] S. J. Wenze and I. W. Miller, “Use of ecological momentary assessment in mood disorders research,” *Clinical Psychology Review*, vol. 30, no. 6, pp. 794–804, 2010.

BIBLIOGRAPHY

- [90] M. S. Businelle, P. Ma, D. E. Kendzor, L. R. Reitzel, M. Chen, C. Y. Lam, I. Bernstein, and D. W. Wetter, “Predicting Quit Attempts Among Homeless Smokers Seeking Cessation Treatment: An Ecological Momentary Assessment Study,” *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, vol. 16, no. 10, pp. 1371–1378, 2014.
- [91] C. Garcia, L. Zhang, K. Holt, R. Hardeman, and B. Peterson, “Latina Adolescent Sleep and Mood: An Ecological Momentary Assessment Pilot Study,” *Journal of Child and Adolescent Psychiatric Nursing*, vol. 27, no. 3, pp. 132–141, 2014.
- [92] P. E. Shrout and N. Bolger, “Mediation in experimental and nonexperimental studies: New procedures and recommendations.” *Psychological Methods*, vol. 7, no. 4, pp. 422–445, 2002.
- [93] J. Fan and J. Zhang, “Two-step estimation of functional linear models with applications to longitudinal data,” *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, vol. 62, no. 2, pp. 303–322, 2000.
- [94] P. H. C. Eilers and B. D. Marx, “Flexible smoothing with B -splines and penalties,” *Statistical Science*, vol. 11, no. 2, pp. 89–121, 1996.
- [95] S. N. Wood, “Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models,” *Journal of the Royal*

BIBLIOGRAPHY

- Statistical Society: Series B (Statistical Methodology)*, vol. 73, no. Part 1, pp. 3–36, 2011.
- [96] A. E. Ivanescu, A.-M. Staicu, F. Scheipl, and S. Greven, “Penalized function-on-function regression,” *Computational Statistics*, Dec. 2014.
- [97] M. W. McLean, G. Hooker, A.-M. Staicu, F. Scheipl, and D. Ruppert, “Functional Generalized Additive Models.” *Journal of Computational and Graphical Statistics*, vol. 23, no. 1, pp. 249–269, Jan. 2014.
- [98] H.-T. Thai, F. Mentré, N. H. G. Holford, C. Veyrat-Follet, and E. Comets, “A comparison of bootstrap approaches for estimating uncertainty of parameters in linear mixed-effects models.” *Pharmaceutical statistics*, vol. 12, no. 3, pp. 129–40, 2013.
- [99] Y. Benjamini and Y. Hochberg, “Controlling the false discovery rate: a practical and powerful approach to multiple testing,” pp. 289–300, 1995.
- [100] B. R. Logan and D. B. Rowe, “An evaluation of thresholding techniques in fMRI analysis,” *NeuroImage*, vol. 22, no. 1, pp. 95–108, 2004.
- [101] J. Pearl, “Direct and Indirect Effects,” in *UAI’01 Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*, no. 1992. San Francisco, CA, USA: Morgan Kaufmann Publishers Inc., 2001, pp. 411–420.
- [102] J. M. Robins, “Marginal Structural Models versus Structural Nested Models as

BIBLIOGRAPHY

- Tools for Causal Inference,” in *Statistical Models in Epidemiology: The Environment and Clinical Trials*, M. E. Halloran and D. Berry, Eds. New York, NY: Springer-Verlag, 2000, pp. 95–134.
- [103] T. R. Ten Have and M. M. Joffe, “A review of causal estimation of effects in mediation analyses.” *Statistical Methods in Medical Research*, vol. 21, no. 1, pp. 77–107, Mar. 2012.
- [104] M. E. Sobel and M. A. Lindquist, “Causal Inference for fMRI Time Series Data with Systematic Errors of Measurement in a Balanced On / Off Study of Social Evaluative,” *Journal of the american statistical association*, vol. In press, 2014.
- [105] M. A. Lindquist, “The Statistical Analysis of fMRI Data,” *Statistical Science*, vol. 23, no. 4, pp. 439–464, Nov. 2008.
- [106] N. a. Lazar, *The Statistical Analysis of Functional MRI Data*, 2008.
- [107] A. D. Craig, K. Chen, D. Bandy, and E. M. Reiman, “Thermosensory activation of insular cortex.” *Nature neuroscience*, vol. 3, no. 2, pp. 184–190, 2000.
- [108] J. C. W. Brooks, T. J. Nurmikko, W. E. Bimson, K. D. Singh, and N. Roberts, “fMRI of thermal pain: effects of stimulus laterality and attention.” *NeuroImage*, vol. 15, no. 2, pp. 293–301, 2002.
- [109] L. Y. Atlas, N. Bolger, M. a. Lindquist, and T. D. Wager, “Brain mediators of

BIBLIOGRAPHY

- predictive cue effects on perceived pain.” *The Journal of Neuroscience*, vol. 30, no. 39, pp. 12 964–77, Sep. 2010.
- [110] S. R. Cole and M. A. Hernán, “Fallibility in estimating direct effects.” *International journal of epidemiology*, vol. 31, no. 1, pp. 163–5, Feb. 2002.
- [111] I. Shpitser and T. J. VanderWeele, “A complete graphical criterion for the adjustment formula in mediation analysis.” *The international journal of biostatistics*, vol. 7, no. 1, p. 16, Jan. 2011.
- [112] K. Imai and T. Yamamoto, “Identification and Sensitivity Analysis for Multiple Causal Mechanisms: Revisiting Evidence from Framing Experiments,” *Political Analysis*, pp. 1–31, Jan. 2013.
- [113] P. Pauli, H. Rau, P. Zhuang, S. Brody, and N. Birbaumer, “Effects of smoking on thermal pain threshold in deprived and minimally-deprived habitual smokers,” *Psychopharmacology*, vol. 111, no. 4, pp. 472–476, 1993.
- [114] J. D. Lane, J. C. Lefebvre, J. E. Rose, and F. J. Keefe, “Effects of cigarette smoking on perception of thermal pain.” *Experimental and Clinical Psychopharmacology*, vol. 3, no. 2, p. 140, 1995.
- [115] A. C. Davison and D. V. Hinkley, *Bootstrap methods and their application*. Cambridge university press, 1997, vol. 1.
- [116] C. De Boor, “A practical guide to splines,” *Mathematics of Computation*, 1978.

BIBLIOGRAPHY

- [117] L. Stefanski and J. Cook, “Simulation-extrapolation: the measurement error jackknife,” *Journal of the American Statistical Association*, vol. 90, no. 432, pp. 1247–1256, 1995.
- [118] S. van Buuren and K. Groothuis-oudshoorn, “mice : Multivariate Imputation by Chained,” *Journal of Statistical Software*, vol. 45, no. 3, pp. 1–67, 2011.

Vita

Yenny Gabriela WEBB VARGAS

PERSONAL DATA

ADDRESS: 615 North Wolfe Street, Room E3040. Baltimore, MD 21205-2179 PHONE: +1 (410) 614-5126 | +1 (443) 509-5788
EMAIL: yennywebb@gmail.com WEBPAGE: yennywebbv.weebly.com

PROFILE

Biostatistician (PhD Candidate) and data analyst. Expert in causal inference and mediation methods as applied to brain imaging and functional data/time series. Proficient in survey analysis, designs of observational studies, and design of clinical and neuroscience experiments. Biostatistics consultant and instructor. I have contributed to research in neuroscience, epidemiology, breast oncology, medicine, and biotechnology.

EDUCATION

JUNE 2015 (Expected) PhD in BIostatISTICS (GPA: 3.51/4.00), **Johns Hopkins Bloomberg School of Public Health**, Baltimore, USA
DEC 2009 Master of APPLIED STATISTICS (Hons, GPA: 96.9/100), **Instituto Tecnológico y de Estudios Superiores de Monterrey**, Monterrey, Mexico
JULY 2007 Bachelor of Science in CHEMISTRY, BACTERIOLOGY, and PARASITOLOGY (Hons, GPA: 97.8/100), **Universidad Autonoma de Nuevo Leon**, Monterrey, Mexico

RESEARCH EXPERIENCE IN STATISTICS

Research Assistant at **JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH**, Department of Biostatistics

09/2013 - *Researcher with Dr. Martin Lindquist on neuroimaging statistics*
Current
Examined the brain response to thermal pain
- Developed a method for mediation analysis for functional data using non-parametric methods, implemented it in R, and wrote a manuscript
- Created a method for causal mediation analysis that uses randomization to identify causal parameters, implemented it in R
- Lead and submitted a joint paper on the role of big data in neuroimaging
Investigated the neural basis of spelling
- Collaborated, designed the analysis, and analyzed an fMRI experiment by performing correlation analysis and group independent component analysis using Matlab and SPM
Predicted hospital readmission after open ventral hernia repair
- Collaborated, designed the analysis, analyzed data, and revised the manuscript for a method for prediction of risk for hospital readmission after surgical hernia repair using the American College of Surgeons National Surgical Quality Improvement Program database

09/2012 - *Researcher with Dr. Elizabeth Stuart on causal inference*
08/2013
Analyzed the impact of living in disadvantaged neighborhoods in adolescent mental health
- Developed a technique for handling measurement error in covariates that are used in propensity score analysis to ensure statistical validity, implemented it in R, and wrote a scientific paper that won the award for Best Student Paper in 2015 by the American Statistical Association
Designed an experiment for a study on educational policy
- Collaborated and performed matched randomization, based on propensity scores
Correlated child development in children with and without autism spectrum disorder
- Collaborated, design the analysis, and analyzed data from an autism study that compared the development of children in a randomized intervention trial to that of children in a cohort, using multiple imputation and propensity score methods in R
Investigated the mental health of sexual minorities, as well as the impact of tobacco and alcohol availability in the neighborhood
- Consulted with two PhD students in Public Health for interpretation of mediation analysis models

Summer Intern at **NATIONAL CANCER INSTITUTE**, Division of Cancer Epidemiology and Genetics, Biostatistics Branch

06/2012- *Researcher with Dr. Ruth Pfeiffer on methods for breast cancer epidemiology*
08/2012
Studied the epidemiology of U.S. women's breast cancer risk factors and incidence
- Manipulated seven nationally representative epidemiological surveys using SAS
- Evaluated women's breast cancer risk factor information for birth cohorts in seven nationally representative epidemiological surveys using SAS
- Investigated the effect of cohort changes in risk factors on breast cancer incidence in the U.S. using log-linear models in R and SAS
- Co-developed and applied a method for joint modeling of the effect of parity and reproductive risk factors in breast cancer incidence in R and revised manuscript for publication

YENNY GABRIELA WEBB VARGAS, YENNYWEBB@GMAIL.COM

Research Assistant at JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Department of Biostatistics

09/2011 - *Researcher with Dr. Michael Rosenblum on adaptive designs for randomized control trials*

10/2012 Discovered methods for subgroup analysis in clinical trials

- Co-developed an adaptive design that gains power for testing subgroup analyses
- Performed power calculations for the adaptive design using R

Summer Intern at NATIONAL CANCER INSTITUTE, Division of Cancer Epidemiology and Genetics, Biostatistics Branch

06/2011 - *Researcher with Dr. Ruth Pfeiffer on methods for breast cancer epidemiology*

08/2011 Correlated the epidemiology of U.S. women's breast cancer risk factors to breast cancer incidence

- Manipulated five nationally representative epidemiological surveys using SAS
- Evaluated women's breast cancer risk factor information for birth cohorts in seven nationally representative epidemiological surveys using SAS

Statistical Consultant at INSTITUTO TECNOLÓGICO Y DE ESTUDIOS SUPERIORES DE MONTERREY Center for Biotechnology

11/2009 - *Consultant to Dr. Mario Moises Alvarez Laboratory*

08/2010 Evaluated flu vaccine efficacy

- Used multivariate analyses to evaluate a trials for a vaccine for the flu virus H1N1 in animal models and humans

Optimized industrial cell growth and production

- Consulted PhD students for the design of an experiment that used factorial designs, and revised manuscript for publication

Assessed the sensory evaluation of beer

- Consulted PhD student, designed and conducted the analysis used categorical data models for a factorial design, creating graphics and providing assistance with writing thesis results

Research Assistant at UNIVERSIDAD AUTONOMA DE NUEVO LEON, School of Biological Sciences

09/2004 - *Researcher with Dr. Diana Resendez Perez*

07/2007 Studied the molecular biology of breast cancer

- Created a library of RNA and cDNA from breast cancer and normal breast tissue samples
- Selected homeobox genes to study based on scientific literature
- Designed PCR primers, established PCR conditions, and ran PCR analysis for 10 genes
- Wrote thesis manuscript, and presented results at a conference

TEACHING EXPERIENCE

Teaching Assistant at JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Department of Biostatistics

Undergraduate level

- **Biostatistics in Public Health Research** with Dr. Scott Zeger and Dr. James Tonascia (Fall 2011), and with Dr. Margaret Taub and Dr. Leah Jager (Fall 2014). Lab instructor, grader, and guest lecturer for 170-student class

Graduate level

- **Statistical Methods in Public Health** with Dr. Marie Diener-West and Dr. Karen Bandeen-Roche (Fall 2013), with Dr. Marie Diener-West and Dr. Jon McGready (Fall 2012), and with Dr. James Tonascia and Mark Van Natta (Spring 2013). Held office hours, grader, consultant for final projects
- **Introduction to the SAS Statistical Package** with Lucy Meoni (Spring 2012). Lab assistant, grader
- **Biostatistics in Medical Product Regulation (online)** with Dr. Mary Foulkes and Dr. Simon Day (Fall 2013). Forum manager, grader
- **Non-Inferiority and Equivalence Clinical Trials (online)** with Dr. Mary Foulkes and Dr. Simon Day (Spring 2013 and 2015). Forum manager, grader
- **Causal Inference in Medicine and Public Health I (presential,online)** with Dr. Elizabeth Stuart (Spring 2014). Lab instructor, grader, guest lecturer. Lab designer, forum manager, grader
- **Tutorial on Matched Randomization (08/2013)**. Course designer, instructor

Associate Professor at UNIVERSIDAD AUTONOMA DE NUEVO LEON, School of Nutrition and Public Health

02/2009 - Co-instructor of the undergraduate courses: **Biostatistics and Scientific Research** and **Medical Biochemistry in Nutritional Evaluation**
06/2010 and Care. Developed and delivered classes, graded, mentored, devised exams and applied them. Two 35-student classes. Co-designed curriculum for 'Biostatistics' for Nutrition majors

Instructor at INSTITUTO SECRETARIAL ADMINISTRATIVO

01/2003 - Instructor of the high school courses: **Chemistry** and **Technology**, grade 11

06/2003 Developed and delivered classes, practices, examinations. Two 17-student classes.

LANGUAGES AND COMPUTER SKILLS

Spanish, English, R, Matlab, SPM, SAS, Minitab, \LaTeX

PUBLICATIONS

- 2015 | **Webb-Vargas, Y.**, Rudolph, K. E., Lenis, D., Murakami, P., and Stuart, E. A. An Imputation-Based Solution to Using Mismeasured Covariates in Propensity Score Analysis. *Statistical Methods in Medical Research* (doi: 10.1177/0962280215588771)
- 2011 | González-Leal, I. J., Carrillo-Cocom, L. M., Ramírez-Medrano, A., López-Pacheco, F., Bulnes-Abundis, D., **Webb-Vargas, Y.**, and Alvarez, M. M. (2011). Use of a Plackett-Burman statistical design to determine the effect of selected amino acids on monoclonal antibody production in CHO cells. *Biotechnol. Prog.*, 27(6):1709-17
- Martínez, H. R., Molina-López, J. F., Cantú-Martínez, L., González-Garza, M. T., Moreno-Cuevas, J. E., Couret-Alcaraz, P., Treviño, S. A., **Webb-Vargas, Y.**, Caro, E., Gil-Valadez, A., Santos-Guzmán, J., and Hernandez-Torre, M. (2011). Survival and clinical features in Hispanic amyotrophic lateral sclerosis patients. *Amyotroph. Lateral Scler.*, 12(3):199-205
- 2010 | Aguilar-Yáñez, J. M., Portillo-Lara, R., Mendoza-Ochoa, G. I., García-Echauri, S. A., López-Pacheco, F., Bulnes-Abundis, D., Salgado-Gallegos, J., Lara-Mayorga, I. M., **Webb-Vargas, Y.**, León-Angel, F. O., Rivero-Aranda, R. E., Oropeza-Almazán, Y., Ruiz-Palacios, G. M., Zertuche-Guerra, M. I., DuBois, R. M., White, S. W., Schultz-Cherry, S., Russell, C. J., and Alvarez, M. M. (2010). An Influenza A/H1N1/2009 Hemagglutinin Vaccine Produced in Escherichia coli. *PLoS One*, 5(7):14

WORK ACCEPTED OR UNDER REVIEW

- 2015 | Nguyen, T. Q., **Webb-Vargas, Y.**, and Stuart, E. A. (2015). Causal mediation analysis with a binary outcome and multiple continuous or ordinal mediators: Simulations and application to an alcohol intervention. *Structural Equation Modeling: A Multidisciplinary Journal* (forthcoming)
- Baltodano, P. A., **Webb-Vargas, Y.**, Soares, K. C., Hicks, C. W., Cooney, C. M., Cornell, P., Burce, K. K., Pawlik, T. M., and Eckhauser, F. E. (2015). A Validated, Risk Assessment Tool For Predicting Readmission After Open Ventral Hernia Repair. *Hernia* (forthcoming)
- Webb-Vargas, Y.**, Chen, S., Fisher, A., Mejia, A., Ciprian, X., Caffo, B., Crainiceanu, C., and Lindquist, M. A. (2014). Big Data and Neuroimaging

CONFERENCES

- INVITED TALKS | Stuart, E.A., **Webb-Vargas, Y.**, Lenis, D., Rudolph, K., Applying multiple imputation with external calibration to propensity score analysis. Joint Statistical Meetings, Boston 08/2014
- Webb-Vargas, Y.**, Lindquist M., Functional Mediation Analysis. Innovations in Design, Analysis, and Dissemination: Frontiers in Biostatistical Methods, Kansas City, 04/2015
- ORGANIZED SESSIONS | **Webb-Vargas, Y.**, Swihart, B. Causal inference in high dimensional settings. ENAR 2014 Spring Meeting, Baltimore 03/2014
- POSTERS | **Webb-Vargas, Y.**, Lenis, D., Murakami, P., Landa, R.J., and Stuart, E.A. Applying multiple imputation with external calibration to propensity score analysis. ENAR 2014 Spring Meeting, Baltimore 03/2014
- Webb-Vargas, Y.**, Stuart, E.A., Sobel M.E., and Lindquist, M.A. Causal mediation with a mediator measured with error. Atlantic Causal Inference Conference, Providence 05/2014
- Webb-Vargas, Y.**, Sobel M.E., Stuart, E.A., and Lindquist, M.A. Within-subjects designs for causal mediation analysis. Joint Statistical Meetings, Boston 08/2014
- Webb-Vargas, Y.**, Sobel M.E., Stuart, E.A., and Lindquist, M.A. Within-subjects designs for causal mediation analysis. ENAR 2015 Spring Meeting, Miami 03/2015
- Webb-Vargas, Y.**, Resendez-Perez D, Reyna-Alvarado DC, Cuaranta-Monroy I, Mar-Aguilar F, Rodriguez-Padilla C. Differential Expression of HOX Genes in Breast Cancer: A1, A5, B13, and D3 as Molecular Biomarkers. Combined Asian Breast Diseases Association, BreastScreen Singapore, Breast Cancer Conference, Singapore 11/2007

AWARDS AND SCHOLARSHIPS

- 01/2015 | **Student Paper Award** sponsored by the Survey Research Methods, Government Statistics, and Social Statistics Sections of the American Statistical Association
- 08/2010 - 08/2012 | **Predocctoral Fellowship** at the National Cancer Institute, Division of Cancer Epidemiology and Genetics, Biostatistics Branch)
- 12/2009 | **Honorable Mention** for Excellence in Academic Activity during the studies in Master of Applied Statistics, Instituto Tecnológico y de Estudios Superiores de Monterrey
- 01/2008 - 12/2009 | **Scholarship for Masters Studies.** Mexican National Council on Science and Technology (CONACyT)
- 06/2007 | **Honorable Mentions** for the Academic Achievement and the Development, Presentation and Defense of the Bachelor Thesis. School of Biological Sciences, Universidad Autonoma de Nuevo Leon
- 09/2006 | **Academic Achievement Award.** Highest GPA of Class 2005-2006, of the School of Biological Sciences, Universidad Autonoma de Nuevo Leon
- 09/2002 - 12/2005 | **Academic Achievement Scholarship.** School of Biological Sciences, Universidad Autonoma de Nuevo Leon

YENNY GABRIELA WEBB VARGAS, YENNYWEBB@GMAIL.COM

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS

American Statistical Association, International Biometrics Society - Eastern North American Region, Association for Women in Mathematics